A controlled two year follow up of neuropsychological status in HIV Seropositive and HIV Seronegative adolescent Haemophiliacs

Thesis accepted for Master of Philosophy at the University of Southampton Department of Psychology

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Ms. P. Westwell kindly gave permission for Miss Viney to include the Birmingham cohort data (originally collected by Miss Westwell during the Haemophilia Project, funded by the MRC) in this thesis.

Dr. R. Pickering generously permitted Miss Viney to draw upon the material in the unpublished paper concerned with the statistical methodology.

Foreword

Foreword – the background to this study

The long delay in the completion of the analysis and writing of this thesis should in no way be seen as a reflection on the University, or the Supervisors, it results solely from DV's personal circumstances and was wholly unavoidable. The two periods of suspension from study were agreed by the University of Southampton. The following is a brief account of the history of this project.

When the current study was planned, apart from a relatively small number of young haemophiliacs, the only children usually thought to be directly affected by the HIV were those vulnerable to vertical transmission, during pregnancy or birth usually from mothers who were IV drug users, or sexual partners of infected users. These children were infected either *in utero* or perinatally – and this infection early in CNS maturation may have been reflected in the specific neurological and other symptoms which they produced and the types of opportunistic infection to which they may be vulnerable. There was interest in determining whether children infected at a later stage of development (during childhood rather than infancy) showed a similar disease course and neurological symptoms.

In 1988-89 Dr. Anthony Aronstam (Director, Haemophilia Centre, Lord Mayor Treloar College, Alton, Hampshire); Dr. Frank G. Hill (Director, Birmingham Haemophilia Centre); Professor Chris Thompson (Consultant Psychiatrist); and Dr. Barbara Wilson (Chartered Clinical Psychologist, specialist in neuropsychology) designed a prospective study of young males with haemophilia and HIV infection. They applied to the Medical Research Council (MRC) for funding to support a quantitative longitudinal study of the neuropsychological and psychiatric status of these young haemophiliacs.

Funding was granted by the MRC and two full time Research Assistants (Pamela Westwell [PW] and Deborah Viney [DV], both Psychology Graduates) were recruited early in 1990. The advertisement for the Research Assistant posts indicated that successful applicants would have the option to register for a Higher Degree in association with the MRC project. This report encompasses the data collected by both Research Assistants, with the permission of PW.

The Research Assistants were given full training in the use of the psychometric tests by Dr. Barbara Wilson and in the use of the Child and Adolescent Psychiatric Assessment (CAPA) by Dr. Richard Harrington (Consultant Child Psychiatrist).

DV was located in Southampton and PW in Birmingham, both were registered with the University of Southampton Department of Psychiatry for M.Phil. / Ph.D.. The original intention was that PW would report the Birmingham data in her thesis and DV would report the Southampton and Alton data.

In addition to the two theses, three papers were planned to report the results of the whole MRC Project (combining the two datasets): a baseline paper reporting the results of the first annual assessment; a methodology paper and a follow-up paper dealing with the three annual assessments.

The data collection took place from Autumn 1990 to August 1993, the final six months (in Southampton only) being supported by an additional grant from the Wessex Medical School Trust. At the end of the MRC and WMST funding (31.08.93) the data collection and data entry had been completed. PW and DV each moved on to work elsewhere.

PW eventually decided not to pursue her own registration for M.Phil. / Ph.D. as she had, by then, begun a Doctorate in Clinical Psychology. PW generously agreed that DV could include analysis of the Birmingham data in her thesis, so that this thesis reports the results of the entire Project.

In the period from Autumn 1993 to February 2001 DV's M.Phil. / Ph.D. registration remained suspended. DV continued on a voluntary basis with the data cleansing; selection of statistical tests; the collation and analysis of the data; and the preparation for publication of the first and second papers as well as the writing of this thesis.

Having agreed a change of Supervisor with the University, DV was able to re-register in February 2001 with the intention of completing the thesis for examination and publication, with the Department of Psychology, under the supervision of Mrs. Sandra Horn.

In Summer 2001 the Psychology Department academic advisers advised DV that the design of this study was not sufficiently powerful to meet the criteria for a doctorate. They advised that, unless she was able to collect more data or to undertake a meta-analysis, the report should be produced for submission as a Masters Degree in Philosophy. Since further data collection was not possible for both logistical and pragmatic reasons and DV did not have any time available (in addition to full time employment in another role) to undertake a meta-analysis, she selected the M.Phil. submission route, though with considerable reluctance given the amount of work already undertaken over a period of more than 10 years.

DV was forced to request a further period of suspension in 2004-05 due to a combination of chronic personal health issues and a work-related difficulty. DV was finally able to re-activate her registration in 2005-06 and completed the thesis by the end of April 2006.

At the end of the official funding in August 1993 the baseline and follow-up data had been collected by DV and PW and entered into the SPSS Data Entry programme. However there had been no time available to clean the data or to analyse it.

The data cleansing, selection of appropriate statistical tests, data analysis and presentation of results undertaken by DV on a voluntary (unpaid) basis and presented in this thesis are the only presentation of the follow-up data and associated analysis from the original MRC study, which would otherwise have had to remain incomplete.

The ways in which this thesis goes beyond the original MRC study proposal include:

- an extensive literature review which covers both the literature available at the time of the original study and a period of more than 12 years past the end date of the original research activity. This places the original study in the context of more recent research findings.
- discussion of the follow-up results
- discussion of the limitations of this study.

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Two year follow-up of neuropsychological status in Haemophiliacs

Deborah Viney

ABSTRACT

Abstract

Research published in the late 1980s from various centres indicated that there could be subtle neuropsychological dysfunctions in asymptomatic HIV Seropositive individuals. It was considered possible that such subtle dysfunctions were an early indicator for the later development of AIDS related dementia. The early research indicated that AIDS related dementia had a characteristic frontal and sub-cortical pattern of damage, with consequences for functioning in specific executive skills. This study was designed to test the hypothesis that young HIV Seropositive Haemophiliacs would produce increasingly poor performance over two years, compared to two control groups in terms of cognitive and psychiatric functioning.

28 male HIV Seropositive Haemophiliacs, infected between the ages 5 to 18 years and aged under 25 years at first assessment for this study, were recruited from three UK Regional Haemophilia Centres. The HIV Positives were compared against two control groups: HIV Seronegative Haemophiliacs [n = 25] and age matched HIV Seronegative Non-Haemophiliacs [n = 12]. All participants were assessed on an extensive neuropsychological test battery and a psychiatric interview. The study design was mixed, having both longitudinal (repeated) measurement and three different groups. Reported here are the comparisons from the three annual assessments for the three groups of participants.

The first annual (1A) assessment, reported in Thompson *et al* (1996), indicated that the HIV Positives were performing overall at least as well as the control groups in all areas, which was contrary to expectations for a group 4-9 years post-HIV-infection.

The follow-up allowed cross-sectional analyses at the second (2A) and third (3A) annual assessments and the longitudinal analysis of the results. This indicated that there was very little psychiatric morbidity, which is consistent with the view (Thompson *et al*, 1996) that the high levels of psychological support provided by the Haemophilia Centres can alleviate the effects of the illness on emotions and behaviour.

The cross-sectional analyses and the longitudinal analysis of the key variables from each test in the neuropsychological battery indicated that the HIV Positive group were performing at least as well as the control groups throughout this study.

Conclusion: *the HIV Positives were performing at least as well as the HIV Negative Haemophiliacs and the Non-haemophiliac Control group in all areas over the two years of the study. Therefore the concern about young Haemophiliac males developing subtle cognitive dysfunction or psychiatric symptoms related to their HIV Seropositivity was found not to be justified for this sample.*

Introduction

Section 1: General Introduction

1.1.1 The aim of this study

In the late 1980s there was a great deal of concern about the possibility that a high proportion of people with HIV / AIDS would develop a dementia. McArthur (1989) suggested a "liberal" estimate that 60% of AIDS patients might develop some form of dementia at some point in their illness. Some studies (e.g. Grant *et al,*1987) had indicated that there might be very early subtle indications of cognitive dysfunction in adults who were HIV Positive but otherwise asymptomatic. It was thought that these changes could be pre-cursors of later major changes in cognitive function (AIDS-related dementia). It was suspected that younger people with HIV might be particularly vulnerable to such minor cognitive dysfunction because of the relative immaturity of their immune systems and nervous systems at the point of infection.

Among the "risk groups" for contracting HIV were:

- people who used intravenous drugs,
- homosexual / bi-sexual men,
- women who were sexual partners of men from the other risk groups
- the children of those women could become infected *in utero* or perinatally or post-natally ("vertical transmission").
- people who received blood products as treatment for conditions such as haemophilia prior to the late 1980s (when the blood supply was secured by the introduction of donor screening and heat treatment of the products). This latter group could become infected at any age, their risk increased

with frequency of treatment and therefore usually with severity of haemophilia.

The effects of the HIV and also of opportunistic infections on the nervous system are various, see later chapters for detailed discussion. In 1990, when the original research for this study commenced, it was unclear what factors affected the expression of the virus in the brain and associated tissues. One possibility was that the child's age, and therefore the extent of maturation of the central nervous system (CNS) at the time of infection, or at the time of becoming symptomatic, could interact with the virus's action, so the "visible" effects could be different at different stages of development.

The "vertical" transmission group are infected very early in the development / maturation of the CNS. The haemophiliac group were older, and therefore one might anticipate a different clinical picture as the CNS is more mature at the point of infection.

Since 1990 a "new" risk group has been identified: children infected by the HIV as a consequence of sexual abuse (Stolar and Fernandez, 1997). Like the haemophiliac group, these young people are infected at a later point of CNS maturation than are those infected "vertically" (i.e. during gestation or peri-natal contact). Brown *et al* (2000) noted that

> *"a developing immune system may be more vulnerable to retroviral infection"* [and, for example] *"HIV dementia progresses more rapidly in*

infants, possibly related to infection during critical windows in early development". (Brown *et al* (2000), p.91)

The existence of such children, with HIV infection acquired post-infancy, heightens interest in the results from the haemophiliac cohort who were infected prior to age 18 years, as they are the only readily available comparators.

In the United Kingdom (UK), haemophiliacs with HIV infection were one group of patients who could readily be contacted, as they were already being monitored through the Regional Haemophilia Centres. The Haemophilia Centres agreed to facilitate the researchers' contact with potential HIV Positive participants who were under 25 years of age and who were believed to have been infected before the age of 18 years. The Centres also facilitated contact with HIV Negative participants and some non-haemophiliac siblings who could act as Controls.

The selection of a group of young men with haemophilia as the study population therefore allows consideration of both the effects of HIV on younger people and also the effects in a cohort who have few other risk factors.

Klein (1998, p. 110) commented:

"Transfusion recipients may be the most valuable group for studying disease progression, because the date of infection is known, and many blood recipients have only a single exposure and lack other potential risk factors."

There are relatively few published subjective reports from people with haemophilia and HIV infection. The (fiction) author Bryce Courtenay published in his book "April Fool's Day" a biographical account of his family's experiences in raising a son with haemophilia who acquired HIV infection. The book includes the full text of a presentation given by his son Damon to a medical conference in Australia. Damon was a close contemporary of the young men who participated in the study reported in this thesis. In view of the heavy quantitative bias in this study and the dearth of such personal accounts and the relative similarity of their experiences, it has been decided to include the full text of Damon's presentation here (see Box 1.1).

Box 1.1

Personal account of haemophilia and HIV infection by Mr. Damon Courtenay (Nov. 1989)

Damon was the son of author Mr. Bryce Courtenay. He was an Australian haemophiliac who acquired HIV infection from infected blood products, and a contemporary of the participants in this study. His story and that of his family features in Bryce's book *"April Fool's Day"* (1993, Penguin Books Australia Ltd.). Damon was born 4th November 1967. He died on 1st April 1991, aged just 23 years, as a result of a massive heart attack due to a cardiomyopathy resulting from HIV infection.

The following is the full text of the paper Damon gave to the *"Children & Adolescents with HIV / AIDS"* conference at the University of New South Wales, Australia on 23 November 1989. It has been transcribed and reproduced here in full with Mr. Bryce Courtenay's explicit permission (pers. comm.) from Chapter 15 (p. 227-233) of *April Fool's Day*.

"Haemophilia is a very difficult disease to live with. It is painful, it is debilitating and it is devious. It strikes when you least expect it. Most people with haemophilia would agree that very few of their bleeding episodes, or "bleeds", are directly related to an actual incident such as a sprain or a fall. Rather, they most often seem to occur spontaneously, for no apparent reason".

"This makes haemophilia a very frustrating disease to live with, as there seems almost no way to prevent bleeds. Of course one doesn't play rugby or get into fights, but even so, leading a normal, everyday existence can bring on the most massive and dreadfully painful bleeds."

"However, there was always one thing about haemophilia, at least in my lifetime, that made it bearable. And that, of course, is that there is effective and relatively fast-acting treatment available. In my lifetime, the treatment of a bleed has advanced from the frozen plasma known as cryoprecipitate to concentrated Factor VIII which comes in powder form. Factor VIII is of course the clotting ingredient in our blood. It has reduced the size of treatment from a 250ml transfusion to about a 60ml transfusion. The concentrate is also easy to store and transport and much more simple to administer".

"So in most cases the worst a bleed would mean was a day or two off your feet or you'd be without the use of an arm or an elbow, a shoulder, knee or ankle, or sometimes all of them."

"Of course, the most difficult part of haemophilia is not the actual time spent in pain through a bleed, but the subsequent arthritic damage caused to the joints. It is the latter which causes most severe haemophiliacs to limp or to lose the full range of movement in one or several joints. It also means that for many, by the time they are fourteen or fifteen, they are in constant pain to a greater or lesser degree."

"Going through puberty with a body that always did look a little different did, of course, have its problems. Girls are naturally curious creatures and invariably there would come a time when you would have to explain why you limped or why you couldn't straighten your arm. Then would come the inevitable question, "Does that mean if you scratch yourself you will bleed to death?" *But a lifetime of learning how to explain your illness meant these questions were explained easily enough and you were accepted as just another guy."*

"How things have changed."

"For the first time haemophilia has become something to hide."

"Because of the constant media attention, many people are aware that the haemophilia community has been severely affected by the HIV virus. And because of the nature of the sickness and the immediate ignorance and the fear it evokes in people, there is a new kind of shame for haemophiliacs to endure. You don't want people to know you have AIDS because you fear rejection. Therefore, you don't want people to know you have haemophilia. So the easiest thing to do is to lie and tell people that you have something else, like chronic arthritis. Now that's fine for people who are new acquaintances, but for all those people who already know you, and know about haemophilia, this approach is no use. So you tell them when they ask – and they do ask – that you were one of the lucky ones, that somehow you were spared. My heart still misses a beat when I tell that lie." Continued....

Box 1.1 - continued
Personal account of having haemophilia and HIV infection by Mr. Damon Courtenay (Nov. 1989) – continued

"That, of course, is only to those you don't want to know. There are friends in whom you have enough confidence to tell the truth. It becomes virtually impossible not to anyway, if and when you actually begin to get ill. But telling friends and having them support you is one of the most vital ways of coping with this threat."

"The point I am making is that for the haemophiliac, it has never been difficult to discuss his disease. After all, it is very like having diabetes, nothing to be ashamed of. But suddenly we must make a choice among all our friends and decide which of them can be trusted with this new information. And it is a very difficult choice to make. Get it wrong and you have to face ignorance & idiocy. But get it right and you create an entire network of support that is vital to coping with personal catastrophe."

"The implications of living with haemophilia and HIV at the same time are immense. Without trying to sound too self-pitying, it is the haemophiliacs who have suffered more than any other group affected by AIDS. This is because we have always had to struggle to stay well anyway, and are usually in a constant state of pain, or at the least, discomfort. Then there are the days when you can't walk or the times when it is impossible to use one of your arms. Combine this with the added threat of AIDS and you have a life which, at times, is very difficult to live."

"It seems that one of the most common problems caused by AIDS is not in itself a life threatening condition, it is simply that you have this general feeling of enormous fatigue, a lack of energy. It is very important that the haemophiliac takes regular exercise, the best form of which is swimming. This is to ensure that as much mobility and flexibility as possible is retained against the crippling effects of joint damage. The will to exercise becomes greatly reduced when energy levels are depleted by HIV. In an indirect way, the presence of HIV in fact makes it a great deal harder to stay on top of the damage caused by the haemophilia itself."

"The next problem is the treatment itself. For some AZT (Azidiothymidine) is absolutely horrible stuff! Its side effects can be absolutely ghastly. For the past two years, since I have been on AZT, I have been chronically anaemic. In addition to the lack of energy caused by the virus, AZT also takes its toll. There are days when even to get out of bed and face a new day becomes a tremendous struggle."

"The anaemia caused by AZT is treatable with a pure blood transfusion, and let me tell you it is like cocaine must be. Suddenly you have energy again, life becomes far more bearable, but soon the haemoglobin drops again and you are left feeling fatigued and frustrated. There is also, of

course, a limit to the frequency of whole blood transfusions. Iron builds up in your system if they are too frequent, which is something to be avoided. So the result is at least half of your life spent with little or no strength".

"Apart from the anaemia, AZT can cause constant nausea in some people. I am one of them. Anti-nausea drugs do have some effect but are far from perfect. It has got to the stage where AZT makes me feel so awful that I only take it every second month. The improvement in the way I actually feel is so great that I am not looking forward to starting back on this toxic substance. However I am grateful to AZT. It seems it has kept me relatively well, although I guess there is a chance I might have stayed well without it."

"Of course, haemophiliacs are not the only ones who have to put up with the imperfections of AZT; however, combined with the pain of joint damage, there are times when, quite frankly, you feel like shit."

"To be quite honest, the concept of dying at the age of twenty-two, or younger, is (virtually) impossible to accept. Certainly you are aware of the facts, of the statistics, but the truth of the matter is – and I have noticed this especially among young people with haemophilia – that deep down you believe that you can escape. You can defy the odds and be the exception to the rule."

"Now the medical evidence may indicate otherwise, and doctors may tell you that you are living on borrowed time. But, with no disrespect intended to those of you from the medical community here today, from my lifelong experience, I can firmly state that we would all be in a lot of trouble if we started believing everything doctors had to say."

"I for one do not intend to die from the effects of this virus. I have developed an attitude which treats this disease as a chronic condition, rather than a terminal one. Perhaps this is because I am accustomed to the concept of a chronic illness and have adopted this attitude as a defence mechanism. But I am firmly convinced that if the mind is strong in its defences against something as potent as AIDS then one's chances of surviving are far greater."

"I said a moment ago that I had noticed that most people with haemophilia were sure that they could defeat this disease or, if not entirely defeat it, at least keep it at bay. This attitude, from my experience in hospital, is less common in gay people. I think this is probably because the concept of protracted illness is less alien to people with haemophilia. They have had to cope with severe disease all their lives and so have less trouble adjusting to the facts of this new condition, AIDS."

"Illness is something to which we have to adjust. It is the success of such adjustment which is the measure of how well we cope with disease. If one person finds that adjustment easier to make than another, is it not logical to suppose that person may find the actual disease less difficult to cope with?"

continued...

Box 1.1 – continued
Personal account of having haemophilia and HIV infection by Mr. Damon Courtenay (Nov. 1989) – continued

"The ability to adjust one's lifestyle and modes of behaviour successfully to take into account that one's body is fighting an invader is the ability to self-cure. I am not talking about a spiritual approach to illness, or even a strictly psychological one. I am talking about a total *attitude, a completely new way of looking at things."*

"It is not in any way a negative concept. To come to terms with reality and adapt yourself in the most effective way, utilising all that you know and all that you are learning, is the key to living the kind of place you want."

"At least, it is the kind of life I want and that is a long and full one."

"Thank you."
[End of text.]

Text reproduced in full by explicit permission of Mr. Bryce Courtenay (Damon's father and the author of "April Fool's Day" which is an account of Damon's life).

1.1.2 Brief introduction to the study reported in this thesis

The research reported in this thesis was planned as a longitudinal comparison over two years of the cognitive performance and emotional health of a cohort of male children and adolescents with haemophilia, all of whom were infected with the HIV between the ages of 5 to 18 years. The data were collected between 1990 – 1993. In order to control for the effects of the HIV, a group of HIV-seronegative haemophiliacs was recruited; to control for the effects of Haemophilia a second independent comparison group of non-haemophiliac boys was recruited.

There were early indications in the literature that HIV related brain damage could be specific to the frontal and sub-cortical structures (Epstein *et al*,

1986). Consequently, in addition to the main battery of tests, it was decided that "frontal lobe" or "executive functioning" in a subset of participants (those from the Alton and Southampton Haemophilia Centres) would be assessed and monitored.

Therefore the general aim of this study was to undertake a quantitative longitudinal analysis of neuropsychological functioning and psychiatric status in three groups of participants (HIV Positive Haemophiliac; HIV Negative Haemophiliac and Non-haemophiliac HIV Negative Controls).

The Experimental Hypotheses and Null Hypotheses are formally stated at the end of the Introductory sections.

1.1.3 Introduction – some general issues in this field of research

The main focus of this study concerns the psychiatric and neuropsychological effects of HIV infection in young people with haemophilia. There follows a brief description of haemophilia and its natural history; and a description of the effects of HIV infection and its natural history, including some reference to the effects of infection in other "risk" groups. Thereafter a more detailed examination of the neuropsychiatric and neuropsychological effects of HIV infection is provided.

For those readers who are not familiar with the structures, functioning and nomenclature of the immune system, a brief introduction to the normal development and functioning of the immune system is included at Appendix 7.

For those not familiar with the general structures of the brain, a similar introduction to the Central Nervous System (CNS) appears at Appendix 8.

In view of the long period elapsed since the design of the study (1988-89); the data collection (1990-93) and the production of this report (2003 -05) the detailed review of the natural history, and particularly the discussion of the literature on the neuropsychiatric and neuropsychological effects, has been divided into two broad periods. The first period summarises the HIV / AIDS literature up to 1990 (when data collection began) and the second section summarises the HIV / AIDS literature published between 1991 and 2005. This decision has been taken to highlight the distinction between the relatively limited knowledge about HIV available at the time the study was designed, and the greater understanding which has developed since 1990. Inevitably, had the study been designed with our current knowledge, it is highly likely that a different approach would have been taken.

In the pre -1990 literature there remained significant doubt about whether subtle cognitive changes could occur at earlier illness stages, particularly in the absence of immunological impairment and other symptoms (e.g. Grant *et al,* 1987). It was also unclear whether such early changes could be predictive of later cognitive dysfunction. This predictability was important because of the number of people thought likely to develop some form of significant cognitive impairment. McArthur (1989) suggested a "liberal" estimate that 60% of AIDS patients might develop a dementia at some point in their illness.

Nadel (1990, cited by Sirois and Hill, 1993) reported that many researchers have described a gradual degradation in behaviour occurring in normally ageing individuals and those with various forms of brain disease or injury. Nadel suggested such behavioural regression might be explicable in terms of the "percolation theory":

> *"It is possible that there might be little observable change in an individual's overt behavior as structural elements in the nervous system are gradually eliminated, but once the system reaches a critical threshold of loss, abrupt changes in behavior become apparent."*
> [Sirois and Hill, 1993, p. 193]

Sirois and Hill suggested that a similar situation may exist for people infected with HIV, with the viral action resulting in gradual CNS changes. One possible mechanism for this damage was identified by Giulian *et al*, (1990) who showed that glial cells infected by HIV could secrete a neurotoxin, which might influence the early CNS development in three ways:

a) by disruption of neurons dependent on glial cells for support;
b) by disruption of the synaptogenic process during peak growth spurts;
c) by disruption of the process of synapse elimination.

These influences, together or separately, could underlie the steady decline in neurological development observed in children with HIV infection.

Several studies identified relatively high rates of psychiatric symptoms, including anxiety, depression (Ostrow, Grant and Atkinson, 1988) and

psychosis (Halstead *et al*, 1988) in adults with HIV infection and it was of both practical and theoretical interest to know whether this was true for infected children. Cognitive functioning / impairment had been found to be a reliable indicator of advancing HIV-related disease in the symptomatic adult population, where it could be used as a clinical indicator of the disease process. This indicator helped to determine when pharmacological intervention was appropriate (Riccio *et al*, 1990; Volberding *et al*, 1990).

Therefore this study attempted to address some of the current concerns about the subtle effects of HIV infection over time in a UK population of younger haemophiliacs, including evaluation of both psychiatric status and neuropsychological functioning. It is important for clinicians to have information about the differing effects of HIV infection on children at different ages, in order that appropriate advice can be given to families and colleagues, and appropriate treatments applied.

1.2.0 Haemophilia

1.2.1 The history of haemophilia and general background including the natural history of the disorder

Haemophilia has been recognised as a condition for all of recorded history: e.g. in ancient times those Jewish boys known to be members of "bleeder" families were excused the rite of circumcision (Jones, 1995). The existence of familial "lifelong bleeding disorders" was noted in the medical literature from at least the 16th century, probably because of a combination of its distinctiveness and the medic's "helplessness" to deal with the consequences of any bleeding (Tuddenham & Laffan (2001)).

The haemophilias are a group of disorders of the blood coagulation (clotting) process, resulting from the absence or reduced production of one or more blood clotting factors, typically Factor VIII (haemophilia A) or Factor IX (haemophilia B) (Jones, 1995; Stehbens et al, 1997). The various clotting factors are all known by their Roman numerals.

Haemophilia C results from Factor XI deficiency (or PTA deficiency) and there are other very rare autosomal recessive forms which result in deficiencies of Factor X or Factor V or Factor VII (Tuddenham and Laffan, 2001).

Other rare inherited bleeding disorders which may result in use of blood products include Factor II (pro-thrombin) deficiency; afibrinogenaemia; dysfibrinogenaemia; Factor XIII deficiency; Factor V plus VIII deficiency; and

hyperplaminaemia alpha-2-antiplasmin deficiency. (Tuddenham and Laffan, 2001)

More commonly, von Willebrand's disease (a platelet disorder resulting from deficiency of von Willebrand's factor) affects more than 100 people per million population in the autosomal dominant form, and 1 person per million population for the autosomal recessive form. (Tuddenham and Laffan, 2001)

1.2.2 The effects of haemophilia

Despite the popular misconception, a person with haemophilia does not bleed any more rapidly than other people. The deficiency of clotting factor means that, when a person with haemophilia bleeds, for any reason, their blood clotting is slower than normal and the bleeding is likely to continue for much longer than would be usual in an unaffected person. Essentially, and especially if the damage which has resulted in bleeding is severe, any bleeding which occurs will not cease until an appropriate coagulant replacement treatment is applied (Youngson, 2000). Similarly any wounds may not heal correctly unless the clotting problem is addressed (Jones, 1995).

Beeton (2002) provided a useful meta-analysis of a number of studies considering quality of life issues for haemophiliacs. This analysis identified that repeated bleeds and associated arthropathy and / or orthopaedic surgery were among the factors which reduced quality of life, as did being HIV positive (though the latter finding was not consistent across all studies). It seems likely that these factors were all associated with experience of chronic and

acute pain and reduced mobility and / or dexterity. One may consider that reduced mobility and dexterity could be the primary factor which affects quality of life, because it tend to reduce individual independence and limit the person's range of activities. Beeton concluded that a valid and reliable quality of life measure specific to haemophilia patients would be needed.

1.2.3 The incidence and aetiology of the haemophilas[1]

The incidence of haemophilia is one per ten thousand population (1: 10,000) and therefore it is relatively rare. There are approximately 2 million haemophiliacs in the world (Koerper, 1989). This may result in delayed diagnosis because other possible explanations, such as extensive bruising being considered a sign of child abuse, are considered more likely (Jones, 1995).

The fact that a Factor VIII deficiency caused Haemophilia A was not known until the late 1930s (Jones, 1995). Factor IX deficiency was linked to Haemophilia B by Biggs *et al* (1952)The aetiology of the main type (A) of haemophilia is well known: the affected single recessive gene is linked to the X chromosome (Youngson, 2000). Haemophilia B has a similar X-linked pattern, but Haemophilia C may be either autosomal dominant or autosomal recessive. Haemophilia C (Factor XI deficiency) is more rare, except for a 5% incidence in people of Ashkenazi-Jewish origin. [Tuddenham & Laffan, 2001].

[1] This section title recognises that haemophilia is a group of disorders rather than a single condition, after this section the conventional use of "haemophilia" rather than "the haemophilias" is observed.

Readers interested in a detailed description of the molecular genetics of the various haemophilias will find such in Tuddenham & Laffan (2001).

Therefore the main types of haemophilia are usually only observed in males, though approximately one third of "carrier" females may have lower than average clotting factor levels which produce some difficulties with heavy menstrual bleeding etc.. Essentially, the defective gene fails to produce the proper blood clotting factors (proteins) in adequate quantities. The main sub-types of haemophilia occur in all ethnic groups at about the same rate.

Inheritance is usually from an affected (carrier) mother: her sons have a 50% risk of being affected by inheriting the X chromosome which "carries" the affected gene. Male haemophiliacs therefore cannot pass the gene to their male offspring, but 100% of their female offspring will be carriers. In the very rare cases of affected females for types A & B, the father will be an adult haemophiliac and the mother a carrier of the gene (Youngson, 2000), though this is usually avoided by genetic testing of potential partners.

Not all cases of haemophilia result from a known familial link, it is thought that spontaneous mutation during reproduction of the X chromosome may account for some cases, possibly up to one third of cases (Jones, 1995; Tuddenham & Laffan, 2001).

It is usual to define the severity of haemophilia according to the patient's "natural" level of the applicable blood clotting Factor (i.e. usually either Factor

VIII or Factor IX). The "normal range" is 50% - 200%. Those with less than 2% of the "normal" Factor level are considered to have a severe form of haemophilia (Youngson, 2000). Those with 3 - 25% are rated "moderate" and those with 26 - 50 % of the "normal" Factor level are considered to be mildly affected. In general the level of severity of haemophilia is also inherited, so that family members tend to have similar severity of haemophilia (Jones, 1995).

1.2.4 The natural history of haemophilia

A person with haemophilia now has a normal life expectancy, provided that appropriate clotting factor treatment is available for any major bleeds (Jones, 1995). This is a significant change in a relatively short time: up until the 1960s most people with haemophilia died during childhood, usually following surgery or other incident which caused bleeding (Jones, 1995). Evatt *et al.* (2002) commented that in the preceding twenty years *"haemophilia care and the type of treatment products used have greatly improved"* (p.221) – though they also acknowledged the emergence of unanticipated risks (of infection) and new complications.

Most people with haemophilia are identified during infancy or childhood when some relatively minor physical trauma results in prolonged external bleeding or very extensive bruising due to internal bleeding (Jones, 1995). An infant with haemophilia is not in any danger during a normal vaginal delivery (Jones, 1995). Where there is no family history of haemophilia to trigger a test on the umbilical blood at birth, the diagnosis is typically made following some minor

trauma (e.g. tear of the tissue joining top lip to gum – in "normal" children the bleeding stops almost immediately, in children with haemophilia it re-starts in the course of ordinary activities). Very often the first diagnosis occurs about the time the child begins to be more mobile and independent, because of the extensive bruising which may result from everyday knocks and bumps.

Rarely, the first indication of haemophilia may be from bleeding into a major organ. For example: one of the participants in the study reported in this thesis had experienced a major vascular incident affecting his brain (intra-cerebral haemorrhage) during infancy, which led to his diagnosis of haemophilia and also resulted in permanent brain damage.

The general experiences of those with haemophilia include a strong tendency to "have a bleed" – i.e. spontaneous bleeding, usually into a joint, occasionally into deep muscle, with no apparent precipitating incident. The person learns to recognise the signs: swelling, tenderness, hot and flushed skin around the joint, sometimes there is spasm of the associated muscles. Often this bleed is associated with pain and where major joints are affected, difficulty with movement. Generally the symptoms resolve after a few days or weeks as the blood is reabsorbed. Often one joint (or more) is affected repeatedly (it is usually known as the target joint), which can create complications such as haemarthrosis (Youngson, 2000). Tuddenham & Laffan (2001) noted that recent research suggests this "targeting" of a single joint may, at least partly, be associated with the synthesis of tissue factor pathway inhibitor (TFPI) in the joint's synovial tissue.

Haemarthrosis is where the body's "scavenging" mechanism [involving phagocytic cells] is triggered, this probably results from the irritation caused by the presence of blood in the synovial tissue. The phagocytes remove the unwanted blood from the joint and in the process create co-lateral damage to the cartilages and other tissues within the joint, eventually producing a painful form of arthritis.

Other complications of haemophilia relate to increased risks (Jones, 1995) from routine dental and surgical procedures and from relatively minor injuries, particularly to the head. A vascular incident in the brain, however caused, can cause anoxia in the affected area and this may have short term (temporary) or long term and permanent consequences for the individual concerned. Brain bleeds are rare, but can be fatal or seriously damaging if left untreated for long. "Bleeds" affecting other major organs can have significant effects (Jones, 1995) for both general health and life expectancy if not appropriately treated.

The consequences of managing the condition may also produce additional risks: for example viral infection of hepatitis or HIV from blood products, addiction to analgesic drugs can become a problem (Jones, 1995). This is most common where "bleeds" affect joints and cause pain, and particularly where haemarthrosis occurs and there may be long term pain.

In the mid 20th century a form of factor replacement treatment was introduced which substantially improved the quality of life of people with haemophilia (Jones, 1995). Initially fresh blood donations were used, later donations of plasma alone were tried. In the early 1960s "cryoprecipitate" was discovered by Pool *et al,* this is a means of retrieving the factors from the blood plasma by freezing. There were also some efforts to use porcine or bovine Factor VIII where human produced stocks were limited, though a proportion of recipients experience inhibitor reactions to animal products. Also in the 1960s, "fractionation" methods of deriving factors from large quantities of blood donations from multiple donors were being developed. The "freeze-dried" concentrates were introduced in the late 1980s and early 1990s. These latter methods mean that multiple donations can be processed to produce relatively small amounts of the important blood clotting factors.

It therefore became possible to temporarily "replace" the missing Factor VIII or Factor IX so that when a "bleed" occurred it could be stopped more quickly and the effects were therefore usually lessened. Unfortunately this treatment is only effective in the short term, permanent replacement of the clotting factor is not yet possible. Factor VIII has a "half life" of approximately 12 hours (i.e. this is the time taken for half of an injected quantity to be used up by the body). The possibility of a permanent cure for haemophilia has been raised: early animal research is underway on effective gene therapies (Jones, 1995).

This factor replacement treatment is highly effective, if highly expensive. It revolutionised the management of haemophilia in industrialised nations

because most people learned to self-treat at home. (Jones, 1995) The introduction of production methods using plasma to produce "recombinant" factor VIII have increased the availability of the blood products to the point where the primary factor limiting treatment is cost (Tuddenham & Laffan, 2001). Ideally all patients would receive regular "prophylactic" treatment with the appropriate blood factor infusions, but infection risks and other considerations have led the haemophiliac community away from that path.

A proportion of people with haemophilia A, about 30% of those with severe factor VIII deficiency and a smaller proportion of those with haemophilia B, have developed "inhibitors" (antibodies) which inhibit the action of the clotting factors by destroying the injected factor. In at least some cases this is an auto-immune failure (Jones, 1995). A few of the participants in the current study had such inhibitors.

In most cases the inhibitors are developed before 10 years of age, though (rarely) they may develop at any point in the lifecycle. Estimates of prevalence are difficult, but overall the cumulative risk for severe haemophiliacs seems to be about 20% by age 5-8 years. A raised incidence amongst siblings suggests a genetic component in the development of inhibitors, as does the observation that patients with certain genetic types are more at risk. [Tuddenham & Laffan, 2001]

1.2.5 Causes of death in haemophilia

Diamondstone *et al.* (2002, p. 660, this work is an aspect of the US Multi-Centre Hemophilia Cohort Study) noted that

> *"historically the primary cause of death for people with haemophilia and other congenital coagulation disorders was uncontrolled bleeding."*

Until the introduction of factor replacement therapies in the mid-20th century, people with haemophilia had a significantly shorter than average life expectancy. By the 1980s their life expectancy was approaching that of the general population.

Since the 1980s, AIDS has taken over as the leading cause of death for those with the infection (Johnson *et al.* 1985; Chorba *et al.* 2001). However, Diamondstone *et al.* also reported the mortality figures for those people with haemophilia who remained sero-negative and found that bleeding was still the leading cause of death (at least in adults). During a follow up period exceeding eight years in a population of 387 haemophiliacs aged over 20 years:

11/25 (44%) of adult deaths were due to haemorrhage;

4/25 (16%) to end-stage liver disease;

3/25 (12%) to stroke;

2/25 (8%) to cancer

and the remainder to various other causes. The prognostic factors included having Haemophilia A and serologic evidence of both Hepatitis B and

Hepatitis C infection which were the same as before the HIV epidemic. Those with a more severe coagulopathy had at least double the mortality risk of the general population. Risk increased still further for those with inhibitors to factor replacements and co-infection with both Hepatitis B and Hepatitis C. Only 12% of HIV negative adults had no evidence of either hepatitis; whereas 70% had serologic evidence of current or past infection with both viruses. [Diamondstone *et al.* 2002]

Diamondstone *et al.* (2002) completed their report by identifying three urgent needs to improve the life expectancy of people with haemophilia:

1. Universal vaccination for Hepatitis B
2. Development of a safe and effective vaccination against Hepatitis C
3. Development of effective and affordable factor replacement products with a low incidence of inhibitor induction.

1.2.6 The risk of viral infection through blood products

One of the risks from blood factor replacement treatment, which was not fully appreciated at first, is the transmission of infections, this resulted from the factor production process involving donations from thousands of people per bottle of concentrate (Jones, 1995). The probability was relatively high that one or more of the donors was carrying a blood-born infection, such as one of the Hepatitis variants or HIV, and hence the entire batch of concentrate could be contaminated without anyone being aware of this (Jones *et al*, 1992).

Tuddenham and Laffan (2001) provided the following list of infections which have been transmitted via factor concentrates:

- Hepatitis B
- Hepatitis C
- Parvovirus B19
- Hepatitis A (in certain concentrates only)
- HIV

In addition to the above list, hepatitis D, E and G have been identified and in December 2003 the announcement came of the first transfusion-associated case of **variant Creutzfeldtt-Jakob Disease** [vCJD] (source: Health Protection Agency [HPA], 2004). It was reported that a blood donor, who was well in 1996 at the time of donation, died from vCJD in 2000. A recipient of this donated blood was diagnosed with vCJD during 2003 and died in the autumn 2003.

The HPA website (2004) also reported a second case vCJD infection by blood in June 2004. The transfusion was received in 1999 from an apparently healthy donor who died from a cause unrelated to vCJD but who tested positive for the prion (within the spleen) at post mortem.

"The possibility that vCJD can be transmitted through blood raises concern about the possible infectivity of blood components and plasma products".

[HPA, 2004, http://www.hpa.org.uk/infections/topics_az/cjd/blood_products.htm#four]

According to the UK's Haemophilia Society website (October, 2004) most people with haemophilia received notice of the potential vCJD exposure in Autumn 2004 from their local Haemophilia Centre. They were advised that some batches of factor concentrate had now been identified as potentially infected due to donors having been diagnosed with the infection some time after donation. They were also informed of a small, theoretical (unproven) risk that, if they had been exposed to vCJD, they could possibly transmit the prion to other people. The situations specified were clinical ones involving invasive medical procedures – there was no mention of sexual or other transmission routes. The risk was identified as additional to that of having eaten beef during the time before BSE was confirmed in British cattle.

Those thought to have been exposed to vCJD were told that they:

"...will not be allowed to donate blood or other tissues and instruments used in certain forms of surgery will not be used on other patients. This will also be included in their medical notes."

"The theoretical risk which has led to these precautions must be put into prospective. The newness of the disease means that little is known about how it can be transmitted so that precautions are based on a worst-case scenario. It is very reassuring that no-one in the world with haemophilia has been diagnosed with vCJD."

[quotes from [The UK] Haemophilia Society website, October 2004]

There follows a short commentary on each of these infections.

1.2.6.1 Hepatitis A

This virus is typically acquired (in non-haemophiliacs) by ingestion of food contaminated with human faeces. There is no specific treatment. It results in inflammation of the liver, but this is usually resolved within 3-6 weeks and it is rare for there to be long-term or chronic liver damage or liver failure. [Youngson, 2000]

Evatt *et al.* (2002) noted that the transmission of Hepatitis A in blood factor recipients may actually have been facilitated by the highly purified nature of the modern factor concentrates possibly because antibodies were removed from the final product.

1.2.6.2 Hepatitis B infection

The Hepatitis B virus is transmissible in a range of body fluids and hence, aside from iatrogenic incidents, there are multiple transmission routes including vertical and sexual transmission. The disease is essentially similar to Hepatitis A but more serious: there is a significant death rate from the acute phase of illness. Approximately 10% of those infected become persistent carriers after the initial stage and many produce complications including cirrhosis and hepatic cancer.

Goedert *et al* (2004) reported that co-infection with Hepatitis B further increases the chances of the HIV positive person developing chronic liver

disease. Among their 2004 study participants, 74% of the HIV positives and 51% of the HIV negatives had evidence of current or previous Hepatitis B infection. A previous prospective cohort study (Goedert *et al*, 2002) found that the risk of decompensated end-stage liver disease [ESLD] was increased more than eight-fold for those who were *current* carriers of the Hepatitis B surface antigen [HBsAg] and over three-fold for those who had *cleared* the antigen. The latter group remain at risk of ESLD in at least two ways: they could have acquired hepatic injury prior to the resolution of their Hepatitis B infection; or they could have "occult" (hidden) Hepatitis B replication at a level only detectable by PCR (Cacciola *et al*, 1999).

Tuddenham and Laffan (2001) commented that many older patients show evidence of past infection by Hepatitis B, but very few remain carriers. They recommended that any haemophiliac without immunity should be offered Hepatitis A and B vaccination.

1.2.6.3 Hepatitis C infection

The Hepatitis C virus was isolated in 1989 and was shown to be responsible for more than 90% of cases of "non-A non-B hepatitis" (Tuddenham and Laffan, 2001). It is a small virus which occurs worldwide with the main transmission routes being IV drug use, tattooing / piercing and needle stick injuries. A minority of those infected develop any symptoms, the disease course is typically mild with jaundice in only 10% of cases. However infection is not a minor matter: 80% of those infected become persistent carriers and of those approximately 33% develop cirrhosis of the liver. [Youngson, 2000].

The origin of Hepatitis C is not known, it has been present in the human population for thousands of years (Goedert *et al*, 2004). Therefore it was almost certainly always a contaminant of the plasma products, in contrast to HIV, which is considered a new pathogen which appeared in the mid-twentieth century. The natural history of Hepatitis C infection is uncertain, especially where there is co-infection with HIV. [Goedert *et al*, 2004]

Serendipitously, the virucidal treatments of blood products intended to control HIV infection had also reduced new Hepatitis C infections almost to zero.

In the UK the screening of donated blood for Hepatitis C antibodies was implemented in 1991. By that time, the sero-prevalence of Hepatitis C was already close to 100% among those who had received regular infusions of either Factor VIII or Factor IX. However the probability of sexual transmission of the virus appears low: only 3% of haemophiliacs' partners were infected. [Tuddenham and Laffan, 2001]

The effect of Hepatitis C infection in haemophiliacs is quite clear: 70% of infected patients have chronic elevation of their liver enzymes and histological evidence of hepatitis; 20% of those with chronic disease will develop cirrhosis and 10% of these will have hepatoma. Progression to liver failure or hepatoma is hastened by co-morbid HIV infection and / or excessive use of alcohol and the treatment of Hepatitis C infection remains problematic,

especially as response to interferon therapy appears to vary according to the genotype of the infection. [Tuddenham and Laffan, 2001].

Approximately 65% of those with Hepatitis C infection in the US and other countries were co-infected by HIV-1. In the HIV positive and Hepatitis C positive population reported by Goedert *et al* (2004) there were signs of potential liver problems: 5% of those over age 41 years had ascites; 8% hepatomegaly and 11% splenomegaly – adjusted for age, this is a 2 – 3 fold increase over the HIV negative population. There was also a high prevalence of sub-clinical conditions which may indicate active Hepatitis C infection or cirrhosis: it is not known whether these will develop into serious disease over time. Only a small minority of these patients had received any treatment for Hepatitis C infection. [Goedert *et al*, 2004]

Goedert *et al* (2004) noted that while most Hepatitis C infections result in both chronic viraemia and chronic hepatitis, there is a proportion of the population (10% - 45%) who show "spontaneous clearance" of the virus and who have normal liver function and histopathology some years after the primary infection. The precipitants of spontaneous clearance are uncertain, but it is likely they include a broad, vigorous, innate possibly cell-mediated immune response. Re-infection after spontaneous clearance is possible and the probability of clearance is reduced in those with repeated exposure and / or HIV co-infection. [Alter *et al*, 1999; Poynard *et al*, 2003; Seeff, 2002; Yee *et al*, 2000; Thomas *et al,* 2000; Kenny-Walsh, 1999; Vogt *et al,* 1999; Ward *et al*, 2002; Mehta *et al*, 2002; Strickland *et al*, 2000]

Among patients in the Haemophilia Growth and Development Study (Daar *et al*, 2001), the clearance rate was only 14.3% for HIV negatives and 2.5% among HIV positives. For an Italian haemophiliac cohort (Yee *et al*, 2000) the clearance rate for HIV negatives was 13.7% and 9% in a mixed HIV positive and negative in the UK (Franchini *et al*, 2001).

Quintana *et al* (2003, p. 605) reported, in their survey of a Spanish Haemophiliac population, that Hepatitis C infection

> *"has been long established as an important cause of death in both HIV-positive and HIV-negative haemophiliacs* [Darby *et al.*(1997); Eyster *et al.*(1999); Lee & Dusheiko (2002)]*"*.

Quintana *et al* added that in their sample the genotypes of the Hepatitis C infections were heterogeneous, 35% of participants had type 1a and 33% had type 1b. Several other sub-types of Hepatitis C were represented in the remaining 32% of their population.

The introduction of effective treatments against HIV infection, such as HAART, has resulted in fewer deaths from AIDS and AIDS related conditions. This has meant that, despite a much lower overall mortality, deaths related to Hepatitis C infection and its consequences have become a larger proportion of the total number of deaths in the haemophiliac population [Sabin *et al.*(2000); Ragni & Belle (2001)]. Although Quintana *et al* (2003) did not report an increase over time in the *number* of deaths relating to liver disease

in their study (because there are fewer deaths overall, liver disease accounts for a greater proportion).

The interpretation of the figures presented by Quintana *et al* (2003) is complicated because of their assumption that patients diagnosed as having "non-A non-B hepatitis" could be considered Hepatitis C positive. Those patients could, instead, have been infected with Hepatitis G, which is clinically silent (unlike Hepatitis C), or one of the other hepatitis virus variants. Nonetheless, Quintana *et al* indicated that in their Spanish sample (n = 383) liver disease related to Hepatitis C accounted for:

- 19% of deaths (7 / 37) before 1988;
- 4% of deaths (1 / 23) during 1988-89;
- 4% of deaths (2 / 48) during 1990-91;
- 4% of deaths (2 / 57) during 1992-93;
- 2% of deaths (1 / 48) during 1994-95;
- 10% of deaths (3 / 33) during 1996-97;

[HAART was introduced around 1997 and resulted in fewer HIV-related deaths and therefore lower overall mortality.]

- 33% of deaths (2 / 6) between 1998 – 2001.

It is important to bear in mind that the active treatment of liver disease in people with HIV infection is complicated because of increased toxicity and treatment interactions with anti-retroviral drugs [Quintana *et al* , 2003].

Goedert *et al* (2004) commented that there was a generally low prevalence of clinical symptoms of decompensated end stage liver disease [ESLD] in their

haemophiliac cohort. This level would stem from the lethality of those symptoms (i.e. anyone reaching that stage simply does not live long). Overall Goedert *et al's* participants, who were recruited to the second Multi-Centre Haemophilia Cohort Study [MHCS-II] because they had HIV-1 and / or Hepatitis C infection, had (adjusted for age) two to three times greater prevalence of ascites, hepatomegaly, splenomegaly and persistent jaundice than other sub-groups, although they noted that such indicators may also be, in part, a consequence of HAART. There were also sub-clinical indications of active Hepatitis C infection or possible cirrhosis. It is not yet known whether these are pro-dromal signs of serious disease, the follow-up research on this is being undertaken.

Although Goedert *et al* (2004) reported that approximately 75% of the US haemophiliac population is chronically infected with Hepatitis C, they also noted that only a minority had received treatment for their infection and that even where treatment is attempted, it is frequently unsuccessful. Hepatitis C genotyping is helpful, since different variants of the virus respond to different treatments e.g. interferon plus ribavirin is more effective against genotypes 2 and 3 than genotype 1 (Fried *et al*, 2002). Goedert *et al* (2004) also noted that non-invasive means to identify those people at greatest risk of serious liver disease remain to be established.

1.2.6.4 Hepatitis D

Youngson (2000) describes "hepatitis delta" as inflammation of the liver caused by a very small virus which can only reproduce when Hepatitis B is

also present. The usual route of transmission is unknown, but this virus has resulted in serious epidemics and is considered endemic in the mediterranean area. Co-infection with Hepatitis B increases the likelihood of a poor prognosis.

Tuddenham and Laffan (2001, p. 621) also made brief mention of a "Hepatitis D virus (delta agent)" which requires Hepatitis B for replication and may also be transmitted by transfusion.

1.2.6.5 Hepatitis E infection

Youngson (2000) reported that hepatitis virus E is a single-strand, non-enveloped RNA virus usually spread by the faecal-oral route. E.g. the first reported major outbreak, in Delhi, India, was the results of flooding contaminated by sewage. It resulted in 30,000 cases of jaundice. The mortality rate is up to 4% in the general population and may rise to 20% among pregnant women.

1.2.6.6 Hepatitis G infection

Relatively recently, another form of infectious hepatitis has been identified by two independent research groups (Leary *et al*, 1996; Linnen *et al*, 1996). It is called by various names, including Hepatitis G [HVG]; non-A non-B hepatitis; and GB virus C [GBV-C].

Hepatitis G is a member of the flaviviridae family and in genomic terms it is similar to Hepatitis C. It appears to be a relatively common infection: its RNA

has been detected in blood samples from approximately 1-2% of the USA blood donor population, suggesting it could be five times more common than Hepatitis C (Alter *et al,* 1997). Other blood donor population surveys have produced a prevalence range from 0.9% in Japan (Masuko *et al*, 1996) to 1.7% in the USA (Alter *et al,* 1997). However some specific populations have higher Hepatitis G prevalence rates:

- IV drug-users: 33 - 49%
- Homosexuals: 11%
- Patients on haemodialysis: 0.9 – 3.1%
- Patients with thalassemia[2]: 18%
- Patients with haemophilia: 18%

(DeFilippi *et al*, 1997; Hanley *et al*, 1998; Yamada-Osaki *et al*, 1998).

Studies of large haemophiliac populations have confirmed that those exposed to factor concentrates derived from large pools of donors are most at risk. For example: 40% of German patients; 48% of American (USA) patients and 52% of French patients had evidence of Hepatitis G infection, compared to far lower rates in those who had only been exposed to products which had been "virally inactivated". [Nubling & Lower, 1996; Yeo *et al,* 2000; Gerolami *et al*, 1997, respectively].

Perhaps the most worrying aspect of the research concerning Hepatitis G is that researchers have found that the various forms of virucidal treatment for blood products have different efficacies: some do not kill all of the viruses

which are now recognised. In particular, some treatments were effective for the lipid-enveloped viruses (hepatitis B and C and HIV) but not against the protein coated viruses such as B-19 parvo-virus (Soucie *et al,* 1998; Kaspar *et al,* 1993; Horowitz *et al,* 1988; Morfini *et al,* 1992). Alonso-Rubiano *et al* (2003) discuss the various techniques and their efficacy in more detail. They added that:

> *"Although there does not appear to be any untoward clinical effect of exposure to or infection with GBV-C [Hepatitis G], the inability to remove the virus using standard viral inactivation technology points to the need for continuing vigilance and improvement in viral inactivation techniques."* [Alonso-Rubiano *et al* (2003) p.114.]

Hepatitis G has been shown to be transmitted by the transfusion route (Schmidt *et al,* 1996). However, it commonly occurs in people who have co-infections by other agents, making it difficult to study Hepatitis G alone. It has been associated with both acute and chronic liver infection. Alonso-Rubiano *et al* (2003) suggested that generally Hepatitis G appears to be either clinically silent or mild, though there are a small number of cases where the infection is associated with more serious symptoms.

The prevalence of chronic hepatic infection in people who receive blood products varies with age, duration of exposure and the type of viral inactivation process used with the clotting factor (Alonso-Rubiano *et al*, 2003). The Hepatitis G viraemia appears to persist for a minimum of 12 months after

[2] Patients with thalassemia receive frequent infusions of blood products and hence they are similar to haemophiliacs in some ways

transmission, but some studies suggest that the viraemia could last 5 – 10 years (Lefrere *et al*, 1996; Wang *et al,* 1996) and a "chronic carrier state" has been suggested by at least one study (Bowden *et al*, 1996). In clinical terms three outcomes have been described: a rapid recovery with eventual clearance of viraemia; a delayed recovery with intermittent elevation of liver function results; and a chronic hepatitis state (usually in cases where there was co-infection by other hepatotrophic viruses). (Masuko *et al,* 1996; Bowden *et al*, 1996; Alter *et al*, 1997).

1.2.6.7 Parvovirus B19

Tuddenham and Laffan (2001) reported that this virus may be transmitted by factor concentrates and that it is not effectively removed by either solvent detergent methods or by heat treatment. Evatt *et al.* (2002) added that its transmission may actually have been facilitated by the highly purified nature of the modern factor concentrates, perhaps because the neutralising or aggregating antibodies were removed from the final product.

1.2.6.8 Variant Creutzfeldt-Jakob Disease (vCJD)

The original Creutzfeldt-Jakob Disease (CJD) is a rapidly progressive neurological disorder primarily affecting middle aged and elderly people which results in death within a few months of onset. Approximately 1% of CJD cases are thought to be iatrogenic, resulting from contaminated surgical instruments and contamination of some body tissues or via contamination of pituitary hormone preparations. At the cellular level it can be seen to be a spongiform encephalopathy which is very similar to Bovine Spongiform

Encephalopathy (BSE). It is associated with an abnormal form of a normal body protein called a prion. There is no effective treatment and approximately 60 cases per year are reported in the UK. [Youngson, 2000]

In the late 1980s a new variant of CJD (now usually labelled vCJD) with a shorter incubation period was identified (Will *et al.* 1996). According to Youngson (2000), up to February 1998 23 of 24 cases had occurred in Britain. There is evidence that this new variant involves the same strain of abnormal prion as BSE. (Youngson, 2000. Evatt et al (2002, p. 222) describe the evidence of a cross-species transmission route as "compelling". Most non-haemophiliac cases are thought to be associated with ingestion of infected beef during the period when the UK supply was contaminated.

Evatt *et al.* (2002) noted that there was, as yet, inadequate technology for a vCJD blood screening programme, though it was expected to become possible in the near future. In the interim, the primary screening measure is selection of donors from countries not involved in the BSE outbreaks.

1.2.6.8 HIV infection

It is thought that the UK concentrate supply became infected with HIV in approximately 1978. The US and UK supplies were still intermixed during this period.

The first cases of illnesses later recognised as AIDS in other populations were in the USA in 1981 (MMWR, 1981). The first cases in haemophiliacs were reported, again in the USA, just one year later (MMWR, 1982).

There is evidence (Kroner *et al*, 1994) of two separable epidemics among people with haemophilia in the USA: the population using Factor VIII were the first infected, mainly in the period between 1978 and 1987, with the peak occurring in 1982. The Factor IX users were typically infected slightly later, between 1981 and 1987, peak around the end of 1983. This difference may have resulted from differing production procedures and later licensing of heat-treated Factor IX products. By the end of 1987, 78% of the regular recipients of Factor VIII and 37% of Factor IX recipients were infected with HIV-1. [Goedert *et al,* 2004].

Goedert *et al* (2004) commented that the incidence of new infections fell rapidly for several reasons:

i. nearly all regular users were infected by the end of 1982

ii. once the risk was recognised, donors with high infection risk were excluded from the donor pool

iii. heat treatment of concentrates and other virucidal measures became standard clinical practice

iv. Actual screening of donated blood and plasma for HIV-1 was implemented in 1985.

Typically, younger haemophiliacs were exposed to the HIV risk for a shorter period than were older people. Anyone with more severe haemophilia, who therefore had more frequent treatments by concentrate, will have had a greater exposure (Brookmeyer and Goedert, 1989).

A sensitive and specific diagnostic test for HIV-1 became available in 1984, so screening of donated blood and plasma was implemented in the USA in March 1985. The comparable diagnostic test for Hepatitis C was not available until 1989. [Goedert *et al*, 2004]

The longitudinal research on people with HIV and haemophilia has proven useful for studying the natural history of HIV infection, particularly as the approximate date of sero-conversion is usually known. Tuddenham and Laffan (2001, p. 620) mention one large cohort study (not identified explicitly) in which there was a 46% rate of progression to AIDS 12 years from sero-conversion.

A small number of studies have focussed on the behaviours necessary to successfully manage living with HIV infection: for example Butler *et al.* (2003) reported a "safer sex" project designed to change sexual behaviour in young sero-positives. This was especially important since this cohort form a significant proportion of young people with HIV infection. E.g. in 1990 adolescents and young adults with haemophilia were the largest group of young people with AIDS in the USA (CDC, 1992).

In general, the treatment of HIV infection in people with haemophilia does not differ from that of other HIV patients, there is one notable clinical exception in that haemophiliacs do not generally appear to be prone to Kaposi's sarcoma, which is presumed to result from another infectious agent (Tuddenham and Laffan, 2001).

Since HAART (highly active anti-retroviral therapy) was introduced for HIV infection in approximately 1997, there has been a significant reduction in HIV progression to AIDS and in deaths in all transmission groups [Detels *et al.*(1998); CASCADE Collaboration (2000); Palella *et al.*(2001); Perez-Hoyos *et al.*(2003); all cited by Quintana *et al.*(2003)]. However Evatt *et al.* (2002) noted that the early HAART regimes involved some of the first Protease Inhibitor (PI) drugs and these were associated with increased bleeding among HIV positive haemophiliac patients (the mechanism for this remains unexplained though several hypotheses have been put forward). The newer drug regimes using later PIs did not show this side effect.

1.2.7 Effectiveness of infection prevention measures

Transmission of both Hepatitis B and HIV infection has been rare in the UK since the introduction of donor screening and heat treatment of blood products in the mid-1980s. In the USA various donor selection measures, purification and virucidal treatments of clotting factor concentrates (for HIV) were introduced in the mid-1980s. Alonso-Rubiano *et al* (2003) reported that since 1990 Hepatitis B and C transmissions by this route have been reduced to virtually zero.

1.2.8 Young Haemophiliacs with HIV infection in the UK

The current study focussed on people with haemophilia who were under age 25 years when infected with the HIV. The UK national records show that by the 31st December 1989 (the start of the current study) there were 392 males, aged 25 years or under, in England, who

(a) had been infected by the HIV where the probable transmission route was blood factor treatment and

(b) were still alive.

Source: The UK Centre for Disease Surveillance and Control (CDSC, 2004) London [Pers. comm.].

The following sections include more information about the general effects of HIV infection in the haemophiliac group and other populations.

More detailed reports of the studies of the neuropsychological consequences of HIV infection in haemophiliac populations are described in the section on the neuropsychological effects of HIV.

1.2.9 The long term effects of haemophilia on a person's cognitive development

As far as was known prior to the occurrence of HIV infection, there is nothing about haemophilia itself which automatically leads to cognitive difficulties. In the past families and medical staff have sometimes tended to protect a young person with haemophilia, for example putting him to bed for days or weeks following a bleed (Jones, 1995). This had consequences in

terms of missed schooling, which could have effects on the boy's educational achievement. However the modern replacement factor treatment regime carries far fewer of these consequences and it has become apparent that most boys are capable of normal schooling and intellectual development. The only exceptions to this occur where there is a second condition in addition to the haemophilia, or where the secondary consequences of haemophilia, such as "brain bleeds" (cerebro-vascular incidents) have long term effects, as they would in any person.

Stehbens *et al.* (1997, p.118) commented:

"The potential neurodevelopmental effects of hemophilia itself, including the potential effects of repeatedly receiving factor concentrate and having sub-acute central nervous system bleeding, are as yet unexamined. Efforts to assist children with hemophilia and their families have been hampered by the general lack of information on the neurodevelopmental effects of both hemophilia and HIV-1 disease."

Stehbens *et al* (1997) noted many of the methodological problems which characterise much of the research on chronic childhood illness:

- Heterogeneity of the medical diagnoses included in many studies
- Over-reliance on retrospective reports
- Limited neuropsychological parameters evaluated
- Limited power to detect differences because of limited sample sizes
- Heterogeneity in the treatment parameters

- a general lack of attention to non-treatment, non-illness variables which can influence outcome
- lack of adequate control groups for comparison purposes.

Stehbens *et al.*(1997) also commented on the importance of the haemophiliac cohort to HIV / AIDS research:

- Most haemophiliacs do not have the risk factors experienced by most children with vertically acquired infection, such as parental drug use, extreme socio-economic disadvantage and "failure to thrive", any of which may result in neuro-behavioural difficulties which are independent of HIV infection.

- Those recruited through the US Hemophilia Treatment Centres receive regular, documented medical care, including psychological and social services, making it less likely that lack of support services contributed to any difficulties they may have. Thus where neuro-behavioural changes do occur, it is likely these are associated with HIV-1 infection or haemophilia rather than any avoidable variables.

- The study of children and adolescents with haemophilia and HIV infection makes a virtually unique contribution in that their age of infection lies between those of the perinatally infected children and adults who have acquired HIV. Consequently, when compared with other age groups, they offer an opportunity to research how the child's neuro-developmental

maturity at the time of infection and their subsequent progress are linked to the course of disease progression.

A very small number of studies have considered the effects of HIV infection on young people with haemophilia. These studies will be mentioned briefly here. They are described in greater depth and evaluated in Introduction section 4.

Mitchell *et al* (1993 - the US Hemophilia Growth and Development Study) reported that among N = 310 boys abnormal MRI fundings occurred in:

15.3% of HIV negative haemophiliacs

17.0% of HIV positives with CD4+ count at or above 200

29.4% of HIV positives with CD4+ count below 200.

Hilgartner *et al* (1993 - the US Hemophilia Growth and Development Study) that the HIV positives were 50% more likely to show scores one standard deviation or more below expected levels in 3 of 9 functional areas although this was not statistically significant compared with the HIV negative group. They commented (p. 208):

"Lowered neuropsychological test performance in both [HIV positive and HIV negative haemophiliac] *groups may be attributable to the deleterious effects of chronic illness."*

Loveland *et al* (1994 - the US Hemophilia Growth and Development Study) reported baseline neuro-developmental findings in which both groups had mean scores in the average range, and any differences in performance of the HIV positive and HIV negative groups were not statistically significant (and not related to CD4+ levels). However approx. 25% of all participants showed below average performance in at least three areas. It was noted that

> *"Academic and adaptive skills were lower than expected based on mean IQ scores, and more behavioural /emotional problems than expected were reported by parents."* (p. 223)

And

> *"Results suggest that the subjects with HIV were relatively free of HIV-related neuropsychological impairment at baseline and that observed differences from general population reflect effects of hemophilia as a chronic illness."* (p.223)

Mitchell *et al* (1997 - the US Hemophilia Growth and Development Study) noted that haemophilia itself produced progressive abnormalities of gait, co-ordination and motor function (in their HIV negative group). However they also reported that immunologically stable HIV positive did not differ from the HIV negatives and that their immune compromised group had high rates of neurological

abnormalities over time and that these abnormalities were common among those who later died.

Smith *et al* (1997) compared HIV positive and HIV negative haemophiliacs with a sibling control group and discussed the importance of the finding that all three groups were under-achieving academically compared to their potential (estimated from Full Scale IQ scores). This finding has been reported elsewhere for haemophiliacs [Colegrove and Huntzinger, 1994; Loveland *et al*, 1994; Woolf *et al*, 1989]. The Smith *et al* study extended this to include the siblings of haemophiliacs and is based on objective psychometric assessments rather than parental reports.

The **Sirois *et al* (1998)** study (reported in more detail in the section of the introduction dealing with neuropsychological effects of HIV infection) indicated clearly that their HIV negative control group of haemophiliacs had a range of difficulties on neurological and neuropsychological examination.

To summarise the long term cognitive effects of haemophilia on cognitive function: until the occurrence of the HIV crisis, the difficulties in schooling / cognitive function experienced by some haemophiliacs were typically attributed either to the consequences of previous intra-cerebral bleeds or to the effects of irregular school attendance resulting from treatment for haemophilia. It is only since HIV negative haemophiliac control groups have been shown to exhibit some mild cognitive dysfunction that there has been consideration of the possibility that either haemophilia itself, or the resulting

bleeds, or regular Replacement Factor treatment may influence cognitive function. Since this is a recent realisation, thorough research to ascertain the precise nature of the cognitive dysfunction, and the mechanisms which create it, has yet to be completed.

Introduction Section 3:
Human Immunodeficiency Virus [HIV] and Acquired Immune Deficiency Syndrome [AIDS]

For those readers unfamiliar with the functioning of the immune system a detailed summary has been placed at Appendix 7. There is also a summary of the structure and function of the nervous system at Appendix 8.

1.3.1.0 A brief history of HIV infection:

"No other subject of medical or scientific enquiry has ever stimulated such a profusion of published information so rapidly as AIDS. By the latter half of 1988 the number of articles catalogued in the [US] National Library of Medicine AIDS Bibliography reached nearly 500 per month. Fortunately, exponentially accumulating information has been an extremely effective weapon in the war against this infectious disease."

Preface, Kaslow & Francis (1989a).

The earliest cases of HIV infection in industrial nations probably occurred during the 1960s, though these were not recognised as connected with later cases for some time (Klimas, 2000). It is thought that the earliest cases of all occurred in sub-Saharan Africa (Kirkwood and Lewis, 1983). Although there is little hard evidence of this, one study did find that serum taken in 1976 from residents of small villages & Kinshasa in Zaire (Nzilambi *et al,* 1988) carried HIV-antibodies. This serum evidence was considered support for earlier observational reports (e.g. Nahmias *et al,* 1986; Nemeth *et al*, 1986) and increased the suspicion that the virus had existed in Africa for some years (Kaslow & Francis, 1998). Wolfe *et al* (2004) have recently reported on naturally acquired simian retroviral infections among African hunters, which may suggest one acquisition vector.

Kaslow & Francis (1989b and 1998) discussed the various hypotheses on the origins of the virus and concluded that the two most plausible theories were:

1. HIV-1 derives from a simian or other animal infection (Lewin, 1985), which has transferred relatively recently, probably via a bite, to the human population, in whom it is especially dangerous.
2. Genetic material which closely resembles HIV-1 existed unobtrusively for ages in some relatively remote human population until someone outside that population acquired the virus from someone within (Desmyter *et al,* 1986).

Kaslow & Francis (1989b and 1998) considered it less likely that the virus arose by genetic mutation or other means. They also noted that *"once it [the virus] appeared in an urban area - could have been almost any city in the world – it became a matter of when, not whether, the combination of multiple sexual partnerships and exchange of contaminated blood would lead to the earliest cases of AIDS."* (p.88, 1998).

The incidence of cases of a then unidentified, but fatal, illness grew steadily throughout the 1970s and early 1980s. It seems that the USA is often the first population in which "new" diseases are noted, probably because it has a relatively large population (so even if the percentage incidence is low, the number of cases is relatively large). Also the health care infrastructure is relatively strong (so unusual illness and death tenda to be noticed and

reported to the authorities). The US also has relatively high availability of research funding, which allows for investigation of the specific disease.

The US Centres for Disease Control (CDC, 1981a & b) reported the first American cases and began surveillance for opportunistic infections & Kaposi's Sarcoma in the presence of unexplained immune deficiency, hence the early label: "Acquired Immune Deficiency Syndrome" (AIDS). The earliest surveillance definition (CDC, 1982b, p.507-8) was: *"a disease, at least moderately indicative of a defect in cell mediated immunity, occurring in a person with no known cause for diminished resistance to that disease."*

In the late 1970s and early 1980s the probability that AIDS resulted from an infection was recognised. Later there was also recognition that it was potentially transmissible by blood / blood product transfusion as well as the other recognised routes (vertical transmission from mother to child during pregnancy or birth; sexual transmission; intravenous transmission).

Doctors in the USA identified the first *clusters* of cases amongst male homosexuals, intra-venous drug users and Haitians in the late 1970s and early 1980s. The haemophiliac cohort were not recognised until July 1982 (CDC, 1982a) in the USA when three haemophiliac men were identified with no other transmission risks, two of whom lived in particularly low AIDS incidence areas. The clear link to blood products was an important indicator that this disease could be a blood borne infection.

The Acquired Immune Deficiency Syndrome (AIDS) was first described in Gottlieb *et al* (1981) and Masur *et al* (1982). The Human Immunodeficiency Virus (HIV) was first identified in 1983[1] by Dr. Francoise Barre-Sinoussi at the Pasteur Institute in Paris (Barre-Sinoussi *et al* (1983).

[Note: at that time it was known as *"Lymphadenopathy associated virus" [LAV]* because it was isolated from a patient with Persistent Generalised Lympadenopathy (PGL).]

Also in 1983, an [2]American group isolated from AIDS patients a virus they labelled *"Human T cell Lymphotropic virus, type 3"* (HTLV-III) because of its similarities to HTLV-I and II (Gallo *et al*, 1983). This virus was eventually demonstrated to infect cells from virtually all patients with AIDS.

In 1985 the HIV was confirmed by Barre-Sinoussi as the *causative* virus in AIDS. The new name, Human Immuno-deficiency Virus (HIV), was agreed as the standard nomenclature. The first HIV-1 antibody test kits were licensed in March 1985 (Peterman & Allen, 1989) and by 1989 in the USA all donations of blood were screened.

[1] Information from Youngson, R. (1995, 2000) *"The Royal Society of Medicine Health Encyclopaedia"* published by Bloomsbury Publishing Plc., London. [the formal reference is not given in that text].

[2] This information is offered in Kirkwood and Lewis (1983, p. 118) but the names of the researchers are not given.

1.3.1.1 The Human Immuno-deficiency Virus

The HIV is a *retrovirus* of the *lentivirus* sub-group. Lentiviruses are characterised by a long interval between initial infection and appearance of serious symptoms, in HIV infection this is known as the "asymptomatic interval".

A healthy person has 800-1200 CD4 cells per cubic millimetre of blood. The HIV targets and kills these cells, which are central to the immune response since they signal other cells to function. Daniel *et al* (2004) noted that the viral load and peripheral blood CD4 count are good markers for HIV disease progression. However, Tuddenham and Laffan (2001) noted that the use of the CD4 count has been criticised because it *"may not correlate perfectly with clinical events"* (p. 602-1) but that it remains a useful marker of progression and vulnerability to opportunistic infection. They added that viral load, neopterin and beta-2-microglobulin is now considered a useful marker.

The CD4 cells are apparently killed by various mechanisms. While some authors (e.g. Aceituno *et al,* 1997; Roger *et al*, 1999) favour apoptosis as the main mechanism for CD4 depletion, even after more than 20 years' research, *"the pathogenesis of HIV-induced CD4 depletion is still unclear"* (Daniel *et al*, 2004, p. 94) although they add that it is now accepted that both auto-immune phenomena and apoptosis contribute.

> *"There is evidence that HIV regulates and mediates CD4 depletion by the induction of autoantibodies and autoreactive immune complexes*

(ICs) against CD4+ lymphocytes." [*ibid*, p.94].

Daniel *et al* (1995) reported that IgM autoantibodies form early in the course of HIV infection and apparently deplete CD4+ lymphocytes rather slowly; the "complement-fixing" IgG autoantibodies were produced at a later stage of infection and were more effective in reducing the CD4+ cells.

Furthermore:

"The interpretation of experimental findings is problematic because HIV induces many phenomena ***in vitro*** *that are not observed* ***in vivo.***" [Ibid, p.94].

As the CD4 count falls below 500/mm^3 half of the immune reserve has been destroyed and the patient suffers unpleasant, but not life threatening, minor infections such as cold sores (herpes simplex), thrush, etc.. As the CD4 count continues to fall to below 200 / mm^3 this immuno-suppression leaves the patient vulnerable to a host of (otherwise rare) opportunistic infections such as cytomegalovirus (CMV) affecting the eyes and / or brain or *pneumocystis carinii* pneumonia (PCP). Immune suppression is also associated (particularly in the homosexual cohort) with the presence of Kaposi's Sarcoma – a rare cancer which causes unsightly purple lesions on the skin.

Tuddenham and Laffan (2001) notes that the presence of HIV antigen (such as p24) in blood serum is a poor prognostic sign and usually occurs late in the disease.

Like all viruses, the HIV can replicate only by entering a cell and "borrowing" its reproductive machinery. Retroviruses have genes composed of RNA

(ribonucleic acid) molecules instead of DNA (deoxyribonucleic acid) like most organisms. Once inside a cell, the retrovirus uses the enzyme reverse transcriptase to convert its single strand RNA into double helix DNA. The virus is thus incorporated into human cells, where it may remain latent for several years. The contaminated DNA produces more of the HIV RNA and the cell then releases large quantities of new HIVs which quickly infect other cells. (Klimas, 2000).

HIV diversity – HIV-2 and other sub-types

Two genetically distinct forms of HIV have been identified, HIV-1 being the more common in the USA, Europe and central Africa. HIV-2 occurs mainly in western Africa and is very similar to HIV-1 (having a similar tropism for immune cells and consequent symptoms) but HIV-2 is more closely related to the Simian Immunodeficiency Virus (SIV) [Klimas, 2000].

The virus is capable of rapid mutation and the genetic variation for HIV-1 is "extremely high" (Klimas, 2000, p.4). This genetic variation and rapid mutation makes the development of an effective vaccine particularly difficult.

"HIV and other lenteviruses are characterized by rapid generation of biologically altered variants, or "quasispecies". In addition, broad sub-groups, classified as "clades", have been defined by nucleic acid sequence analysis for both Hiv-1 and HIV-2 (Korber et al, 1994; Gao et al, 1994). Viral strains consisting of recombinations of different subtypes have also been described.

Some of these variants will undoubtedly escape detection by the contemporary donor screening assays." [Klein, 1998, p. 110]

In 1986 researchers described a second virus (designated HIV-2) causing AIDS. It was found to be relatively common among West African sex workers (Clavel *et al*, 1986). HIV-2 has also been reported in Europe in both transfusion recipients and haemophiliac men (Dufoort *et al,* 1988; Simon *et al,* 1989). HIV-2 infection is rare in Western Hemisphere blood donors – in the USA since 1992 in over 7 million tests on donated blood / plasma, just three HIV-2 cases have been identified (CDC Update 1992). So far, the CDC reports no transfusion-transmitted HIV-2 cases in the US. The CDC's models estimate the HIV-2 prevalence among US blood donors as 0-3 infected units per 10 Million screened donations (O'Brien *et al,* 1995).

Nine HIV subtypes (labelled by letters A - H, plus O[3]) have been identified and can be mapped geographically. Type B is the most common in Europe and the USA [Klimas, 2000].

The first report of the HIV-1 O subtype was in Central and West African patients in 1994 and by 1996 two cases were reported in the USA (FDA, 1996). These variants showed a 65-70% homology with HIV-1 and 56% homology to HIV-2.

[3] HIV sub-type O is closely related to both HIV-1 and HIV-2 and is most often found in Camaroon and Gabon (Africa).

Table 1.3.1.2:
The USA Centre for Disease Control (CDC) stages of HIV infection classification system (1987)
[Morbidity and Mortality Weekly Review (suppl.) 36: 1-9, 1987]
revised [Morbidity and Mortality Weekly Report, 41, 1-19, 1992].

CDC stage	Description / important features
I	Initial infection – may feature a brief experience of high temperature and other non-specific symptoms. Viral culture and / or antibody tests *may* detect the infection.
II	Asymptomatic period (chronic asymptomatic infection)
III	Persistent generalised lymphadenopathy [PGL]. First appearance of HIV related symptoms, hence this is sometimes called the Symptomatic stage –or the AIDS Related Complex (ARC).
IV a	Other diseases – constitutional disease
IV b	Other diseases – neurologic disease
IV c1	Other diseases – specified secondary infectious diseases [includes PCP, CMV and progressive multi-focal leukoencephalopathy, candidiasis (except oral)]
IV c2 (NB: only IV c1 diseases were included in the definition of AIDS]	Other diseases – other specified secondary infections [includes tuberculosis and oral candidiasis].
IV d	Other diseases – secondary cancers
IV e	Other diseases – other conditions
HIV Negative	No infection present

This CDC classification system was revised again (CDC, 1992) – see section on post-1990 literature.

1.3.1.2 The structure of the HIV:

The HIV is an envelope virus, its outer coat fuses with the target cell membrane in order to achieve infection of the cell. The viral envelope (outer coat) is composed of two layers of lipids taken from the human cell membrane when the new virus particle buds from it. The viral envelope consists predominantly of proteins taken from the host cell plus approximately 72 copies of a particular complex HIV protein *("env")* which protrude from the surface envelope. *Env* has a high affinity for the CD4 receptors (making a strong bond) so this is the part of the virus which binds with the CD4 receptors to enter a host cell. *Env* consists of a cap of 3 or 4 molecules called glycoprotein 120 (gp120), plus a stem consisting of 3 or 4 gp41 molecules which anchor this structure in the viral envelope. [Levy, 1993]

The viral core of HIV has two parts: the outer core is a bullet-shaped capsid composed of 2000 copies of a viral protein ("p24"). The capsid surrounds two strands of RNA which each have a copy of the HIV's nine genes. The remainder of the core consists of viral proteins and enzymes essential to various aspects of its life cycle [Levy, 1993].

1.3.1.3 The life cycle of the HIV:

The first stage in viral replication is the **attachment** of a viral particle to the CD4 receptor of a potential host cell. The virus then disgorges its contents into the cell and *protease* enzymes remove the viral envelope, leaving the RNA strands in the cytoplasm of the host cell. (Levy, 1993). Direct cell to cell

infection can also occur, through the CD4-mediated **fusion** of an infected and an uninfected cell (Sato, 1992).

In the cytoplasm of the host cell, *HIV reverse transcriptase* converts viral RNA into a full length copy of the viral DNA ("**reverse transcription**"), this DNA is then degraded into a smaller functional piece (Levy, 1993).
Note: some anti-HIV drugs such as AZT slow the pace of infection by interfering with reverse transcriptase.

The newly created HIV DNA then migrates into the host cell's nucleus, where *HIV integrase* assists in splicing the viral DNA into the host's DNA. This process of **integration** results in the "provirus" form. The cell now has two options: immediate activation, or it can enter a resting state, with HIV integrated in its DNA but not actively replicating until it is activated months or years later. When activated, the cell will begin to manufacture viral proteins. Ho *et al* (1997) demonstrated that most cells are activated and few revert to the resting state. However, there remain a critical mass of infected resting cells in the lymphoid tissue which will maintain a long-term latent infection (sometimes called a *reservoir* of infection) even in the event of highly active anti-retroviral therapy [HAART] and undetectable viremia[4] (Ho, 1998).

The activated cell creates new virus particles by a process of **transcription**: the viral DNA is copied back into messenger RNA (mRNA) which is transported from the nucleus to the host cell's cytoplasm (Levy, 1993).

[4] Viremia is a term referring to the level of active virus which is currently detectable in the blood stream / other tissue.

Once re-established in the cytoplasm, the mRNA co-opts the host cell's protein mechanism and begins to construct the HIV proteins, using the mRNA as a template. This sequence of proteins is **translated** into the RNA and proteins comprising the envelope and core of the virus.

The gene products of the translation process are much larger than necessary for the final virus and must be spliced by *viral protease* into smaller functional units. Once spliced, the viral envelope proteins **assemble** within the host cell's membrane with the core proteins, RNA and enzymes just inside the membrane. The virus then pinches off the host cell and "**buds**" (Levy, 1993), once free of the host cell it is infectious and can infect trophic tissue. Viral particles in their thousands can be produced, either chronically over weeks, or in a single burst resulting in cell death.

The amount of time required for the entire viral life cycle is much shorter than researchers originally thought: Ho (1997) has demonstrated a lapse of just 2.4 days between initial infection and thousands of virions budding from that infected cell. This understanding has emphasised the need for early intervention after possible infection (e.g. by needlestick injury[5]) using protease inhibitors to prevent the infection from "taking" in the body.

Another important development has been the recognition that T cell activation is central to the life cycle of the virus: activated CD4 cells are both the main

[5] The term "needlestick injury" is used in clinical settings to describe an accidental penetrative injury by a sharp object, in particular a non-sterile object which may potentially carry infection.

target of infection and the most efficient viral replicators (Gowda *et al*, 1989; Zack *et al,* 1990). Resting T cells are more difficult to infect and must become activated within 2 days to replicate the virus (Zack *et al,* 1992). Therefore any individual exposed to the virus who already has marked T cell activation (e.g. due to concurrent infection) will develop a high viral burden more rapidly than a person not co-infected.

1.3.1.4 Transmission of the HIV:

In most cases HIV is a **sexually transmitted** disease (STD). The virus crosses the mucosal barrier of the vagina / vulva / penis / rectum by first coming into contact with a group of immune cells, which are permanently located at the mucosa. These are called dendritic cells, they transport the virus across the mucosa and release it, either into the tissues or directly into a lymph node (Klimas, 2000). The virus then binds to a CD4 receptor on a lymphocyte and the infection cycle begins. The risk of infection is greatest in cases where there is concurrent STD, very high viral load (beginning or end of disease) or the sex is sufficiently rough to tear the mucus membranes. Atkins *et al* (1996); Cohen *et al* (1997).

HIV is also transmitted by **contact with infected blood**: most often this occurs in the context of **shared needles or syringes** used for recreational drugs or body-building hormones.

Iatrogenic transmission occurs through infected blood donations or blood products. Transfusion recipients are exposed to only a small number of

donors and their infection risk is consequently the lowest among the major HIV "risk groups" (Peterman & Allen, 1998). In contrast the manufacture of blood products such as Factor VIII is sourced from thousands of donations and hence the risk of any infection is high (as only one donation needs to be infected to contaminate the batch). Therefore the infection risk for haemophiliacs (including non-haemophiliac recipients of blood products) is relatively high. They have a sero-prevalence almost 1000x that of transfusion recipients (Peterman & Allen, 1998), the highest of all HIV/AIDS risk groups.

From 1985 the medical blood supply in the USA, Canada and Europe was screened for HIV and therefore there have been very few infections since that time. The haemophiliac cohort in the current study are believed to have been infected between 1970 – 1985, before the UK supply was screened and before the blood product supply was closed to donations derived from outside the UK.

Since 1985 the further introduction of donation screening and heat treatment of all donations has further increased the security of the supply, though cellular components still represent a small risk, as there are (as yet) no virus inactivation procedures for those components (Klein, 1998).

Klein (1998, p.111) commented:

> *"The reduction of risk of transfusion-transmitted HIV over the past 15 years has been dramatic and reassuring. Nevertheless, enormous public concern persists."*

Peterman & Allen (1998, p.179) added:

"With the development of an HIV-1 antibody screening test, the recipients have become the only AIDS risk group for whom the risk of acquiring infection has been nearly eliminated."

Vertical transmission is the third possible route: pregnant HIV positive women have approximately a 33% risk of transmitting their infection to the child, either during pregnancy, during the delivery or (rarely) when breastfeeding. The introduction of anti-retroviral treatment in pregnancy and during parturition has reduced this risk to less than 10% in the USA (Klimas, 2000). However the US CDC 1998 figures show that 91% of children under 13 years acquired their infection vertically. Blood transfusion (5%) and blood product treatment for haemophilia (3%) account for the remaining cases in under 13s.

Belman (1997) commented that it is not known in which trimester of gestation infection is most likely to occur, nor what proportion of infections occur during gestation and what proportion occur during parturition or breast-feeding. She reported a small number of studies which indicate foetal infection occurring prior to the 20th week of pregnancy (e.g. Jovaisas *et al*, 1985) but added that then-current research (1997) suggested that at least 50% of infections occurred before or during the birth process (e.g. Boyer *et al,* 1994). Belman (1997) noted that several maternal factors increase the transmission risk. These risk factors include:

- low CD4 count,
- high viral titres,

- advanced HIV-1 disease
- placental membrane inflammation
- premature rupture of membranes
- premature delivery
- increased exposure of infant to maternal blood
- and low vitamin A levels.

[Examples: Boyer *et al*, 1994; Burns *et al*, 1994]

Occupational transmission is a risk for health care workers where there is an accidental needlestick or mucosal splash with contaminated material. The risk per incident (needlestick) with appropriate immediate treatment is approximately 0.33% (compared with a 33% risk for contracting Hepatitis B by this route) (Klimas, 2000).

Little is known about the factors which influence the ease of transmission of the virus between individuals (Kaslow & Francis, 1998), though some research suggests that transmissability may increase in the later stages of immunodeficiency (Goedert *et al*, 1987). Other research, by Peterman *et al,* (1988), comparing the seropositive and seronegative wives of infected men indicated that the sero-positive women actually had fewer sexual contacts (though the range of contacts was broad). Kaslow & Francis (1998, p.97) summarised the implications from these analyses as "unknown factors must play a significant role in determining transmissability or susceptability".

1.3.1.5 Preventing the transmission of HIV

Klein (1998) reports that as HIV is a relatively labile, lipid encapsulated virus there are a number of viral inactivation methods available to produce non-infectious plasma derivatives (blood products):

- **Pasteurisation**[6] - heating in solution to 60°c for a period of 10 hours.
- **Use of a solvent detergent**, with or without heat treatment.
- **Vapor treatment**
- **Nanofiltration**
- **Sodium thiocyanate plus ultra-filtration**
- **Immuno-affinity purification**

These techniques will also greatly reduce the risk of transmission of hepatitis, though the non-lipid-encapulated viruses (e.g. human parvovirus B19 and hepatitis A) can still be transmitted.

1.3.1.6 Epidemiology of HIV : The data from the late 1980s

The World Health Organisation [WHO] (cited in Kaslow & Francis, 1989b) provided an early summary of the AIDS statistics then available:
see Table 1.3.1.6 below.

[6] The basic method is the same as for the pasteurisation of milk, but the length of heating and temperature required differ.

Table 1.3.1.6: WHO AIDS data by region, February 1988

Adapted from Kaslow & Francis (1989b)

Area	Number of AIDS[7] cases reported at Feb 1988
The Americas	60,409 including 53,069 in the USA
Africa	9,760 [largest cohort 2,369 in Uganda] 7 countries reported more than 500 cases each.
Eastern Mediterranean	82
Europe	10,245 largest cohort in France, 3,073; UK then had 1,227 cases; only 5 European countries reported more than 500 cases.
Southeast Asia	24
Western Pacific	913 largest cohort Australia: 758 cases
Total	**81,433 cases worldwide**

The WHO 1989 summary indicated that just 10 countries were contributing more than 80% of the reported AIDS cases, though it was recognised that inconsistent reporting and political sensitivities would have seriously compromised estimates of occurrence in many countries.

In 1989 the World Health Organisation projected that by the Year 2000 three million women and children would die from HIV-related disease and ten million children would be born with the infection. [Chin and Mann, 1989; Chin, 1990].

[7] This does not include those who were HIV positive but did not have AIDS.

The United States of America:

In 1988 (29 August) the US CDC (cited in Kaslow & Francis 1989, p. 89) reported a total cumulative number for adult & adolescent AIDS cases of 70,882. Of those AIDS cases 92% were male; 63% of the total were categorised as transmission to a homosexual or bi-sexual male; 680 AIDS cases (1%) were people with haemophilia or coagulation disorder.

In addition for 1988 there were 72,024 US child AIDS cases reported (CDC 1988). Of those cases 91% were male; 67 (6%) were children with haemophilia / coagulation disorder; and a further 150 (13%) acquired the infection by transfusion of blood or its components. The majority of children (78%) acquired their infection from a parent at risk, usually the mother.

At that time there was no generally available direct test for the virus and no disease classification system for those who were HIV-positive but had not yet acquired AIDS, so only estimates of numbers of HIV positive cases were available. Estimates of HIV infection for 1986 - 1987 (CDC, 1988) suggested that:

- 60% (approximately) of the US haemophiliac population were thought to be HIV positive;
- 25 - 45% of the homosexual population;
- 5% of prostitutes;
- 5 – 55% of the IV drug using population (highest in larger cities);
- 0.01% of 3 Million US blood donors;

- 0.84% of heterosexual women attending pre-natal / family planning clinics;
- 0.18 – 1.5% of infants with live births;

Overall it was estimated that in mid-1988 between 1,500,000 to 2,000,000 Americans had been infected [adapted from Kaslow & Francis, 1989b, Table 6.3, page 92].

Other countries:

Kaslow & Francis (1989b) reported that population surveys in "developed areas" (p.95) other than the USA (e.g. Canada, Europe & Australia) indicated that prevalence of HIV-1 infection remained low: usually less than 1% in mid-1988. The first cases reported in Western Europe were in 1981-82, shortly after its appearance in the USA (Blanche & Tovo, 1998). Whereas prevalence rates in parts of the "developing world" (Kaslow & Francis, 1989b, p.95) exceeded 15% in some African urban populations and 10% in Haiti. The WHO estimated that between five million and ten million people had been infected across the world.

Epidemiology in the haemophiliac population: data from the late 1980s

As previously noted, in the USA three haemophiliac AIDS cases were reported in July 1982 (CDC, 1982a). Later estimates suggested that by the time of those first reports, 20% of the haemophiliac population were already carrying the infection (Peterman & Allen, 1989). The first to suggest the possibility of a blood-borne agent were Marx (1982) and an editorial in *The*

Lancet (1983). A meeting convened by the CDC in January 1983 highlighted experts' concerns about a possible infection as a threat to the blood supply and led to significant changes in the practices associated with blood collection & transfusion. The US National Hemophilia Foundation published a series of recommendations (Medical & Scientific Advisory Council, US National Hemophilia Foundation, 1983).

During 1983 additional cases in haemophiliacs and recipients of blood from donors who subsequently developed AIDS were reported. By January 1984 18 AIDS cases were reported in adults, without any other known risk factors, who had received blood transfusion within 5 years of diagnosis. This was compelling evidence, though a causative relationship between the transfusion and the development of AIDS could not be proved. The association did suggest both the possibility of a blood-borne infectious agent and also the possibility of an asymptomatic carrier stage in which donors could appear sufficiently healthy to be accepted as blood donors.

The discovery of the HIV led to the deliberate infection of a small group of chimpanzees with infected plasma components (Alter *et al*, 1984) and thus the creation of a non-human primate model. The virus was also isolated from the cells & plasma of donors and transfusion recipients (Peterman *et al*, 1985).

Within 5 years of the earliest recognised cases, at the end of 1987, n = 592 AIDS cases associated with clotting-factor concentrates had been reported in

the USA. This meant that over 4% of America's 14,000 haemophiliacs had developed AIDS (Hardy *et al*, 1985) and AIDS was the leading cause of death for this population. The HIV infection rates were not reported specifically for that period, however Peterman & Allen (1989) commented that [up to 1989] some 20,000 –30,000 American haemophiliacs had been infected.

In the USA 50% of haemophiliac patients across 100 Haemophilia Centres tested HIV positive between 1985 –1989 having been infected through blood products, most probably between 1981-1984 (Augustnyiak et al, 1991). The rate was 67% for those with severe haemophilia and the rates of infection did not differ across the various regions of the US. Up to 1997 (Stehbens et al, 1997) some 20% of those haemophiliacs (n = 2798) had developed AIDS and a further 1195 cases had occurred in which haemophilia was one of the risk factors.

Retrospective studies (Evatt *et al* (1985) and Goedert *et al* (1985)) indicated that more than 90% of people with severe haemophilia in the USA who had been treated with blood factor concentrates had been infected before 1984.

Haemophiliacs and transfusion recipients have transmitted the infection to their sexual contacts and (perinatally) to their children (CDC, 1987b). Between 5 – 20% of sexual partners acquired the infection (Kreiss *et al,* 1985; Allain *et al,* 1986; Peterman *et al,* 1988). In many cases these transmissions are likely to have occurred before HIV infection was suspected and appropriate protective measures were recommended.

The risk of HIV transmission from a single injection of factor concentrate was not known, though the evidence suggests that it was less than 100% (Peterman & Allen, 1989). Jason *et al* (1986) found that the risk of sero-positivity for 51 recipients of Factor VIII was 75% (38/51), but this was no higher than the risk for a control group with matched clotting factor requirements (44/51 [86%]). Similarly, recipients of specific contaminated batches of Factor IX were no more likely to be sero-positive (9/30 [30%]) than recipients not exposed to the batch which was traced (12/30 [40%]).

Studies providing information on the time taken for sero-conversion to occur are rare, however one Edinburgh cohort (n = 33) were found to have been exposed in April 1984 - reported by Ludlam *et al* (1987). The follow-up schedules were variable, but give an indication:

13/33 (39%) developed antibody within 15 weeks;

1/33 (3%) within 11 – 36 weeks;

4/33 (12%) after more than 20 weeks;

15/33 (45%) remained sero-negative at least until 1987 (2 – 3 years).

The risk of sero-conversion for any person with haemophilia is associated with the amount of exposure to clotting factor (Ramsay *et al*, 1984; Ragni *et al*, 1986). Those with Factor VIII deficiency were more likely to sero-convert than those with Factor IX deficiency, probably because of a higher factor requirement and possibly because of a difference in the efficiency of transmission with the two products. People with higher factor requirement

also had a higher incidence of AIDS, which was thought to suggest that multiple exposure increased the rate of progression, though this could simply have been because greater factor requirement was associated with earlier infection (Peterman & Allen, 1989).

Heat treatment of blood products was introduced in 1986 in the USA (Quinnan *et al*, 1986) and was mostly effective in reducing the risk of transmission. However there were some reports of apparent transmission involving blood products produced before the routine screening of donors (CDC, 1987b), which suggested that the heat treatment method was not 100% effective, at least in the earliest period in which it was used.

The introduction of heat treatment of blood / products plus HIV-antibody screening of donated samples removed virtually all risk of HIV transmission associated with blood donation. The CDC (1997b) reported that up to December 1996 approximately 50 Million patients had been transfused in the USA and only 36 adults and 3 children subsequently developed AIDS after receiving blood which had been screened as negative for HIV antibodies. These cases would almost certainly have resulted from blood received from donors who were recently infected and who had yet to produce antibodies (the time sometimes described as "the window period"). Following these developments Lackritz *et al* (1995) estimated the risk (in the USA) of HIV infection through blood transfusion at approx. 1: 500,000 units transfused.

As previously noted, even for those people known to have been infused with infected blood, the infection risk does not reach 100%. The US Transfusion Safety Study (Donegan *et al*, 1990) of serum samples collected in 1984 found n = 124 recipients of HIV-antibody positive transfusions. By 1990, 90% of the 124 had sero-converted. The remaining 10% were investigated using both viral culture and Polymerase Chain Reaction (PCR) assays, which established that the recipients had not been infected with HIV. However they were apparently not immune to the virus (since their lymphocytes could be infected *in vitro*).

Investigation of cases where sero-conversion did not occur despite (sometimes repeated) exposure is obviously important as it may help to identify host / environmental factors which help to protect against infection. Klein (1998) noted that approximately 10% of haemophiliacs repeatedly exposed to infectious pools of clotting agents did not sero-convert. Klein (1998) suggested that some host factors, plus the virulence of the viral strain, the inoculum size and / or the presence of other infectious agents in the inoculum may have a role in "successful" transmission.

According to Donegan *et al* (1994) the variables which appear to be correlated best with HIV transmission by transfusion are:

- Level of viremia
- Type of component transfused - since HIV is cell associated and also present in plasma, all blood components are potentially infectious.
- Length of refrigerated storage of the blood.

However some host factors have also been identified, including a genetic factor associated with certain chemokine receptors which play a role in the physical process of infection (Dean et al, 1996) by acting as a second ligand for viral entry into CD4 cells.

Other factors continue to be researched for their influence on both infection and clinical course, including:

- Type of viral strain
- Concurrent infection by other blood-borne agents
- Cellular receptors for HIV.

Klein (1998) reported that the CDC has recorded no additional sero-conversions from donor-tested, virus-inactivated factor concentrates since 1986. A survey of 155 patients who were treated with more than 15 million units of pasteurised Factor VIII found no sero-conversions (Schimpf *et al*, 1989).

Klein concluded (1998, p. 109):

"Thus fractionated blood products properly treated with current virus-inactivation procedures carry little or no risk of HIV transmission."

1.3.1.7 Epidemiology of HIV : The HIV / AIDS data 1998 onwards

Worldwide data:

By 1998 more than seven million people (worldwide), including one million children, were HIV positive [UNAIDS, 1998]. This compares with the 81,433 cases worldwide reported in February 1988 by the World Health Organisation [Kaslow & Francis (1989b)].

Africa:

In Africa the Joint United Nations Programme on HIV/AIDS (UNAIDS) / World Health Organisation (WHO) estimated that in 1996-7 some 20.8 Million (68%) of the global total of people living with HIV / AIDS were living in sub-Saharan Africa. They further estimated that 7.4% of all people aged 15 - 49 years living in sub-Saharan Africa were HIV positive. The primary transmission route was heterosexual activity, with vertical transmission and use of unscreened blood providing "secondary" epidemics. More than 20% of pregnant women were HIV infected in some areas. Vertical transmission and breast feeding accounted for more than 90% of paediatric infections. [Greenberg *et al*, 1998]

USA:

In June 1998 the US CDC reported n = 8280 children under 13 years and n = 3302 adolescents (13-19 years) with AIDS; this did not include those with HIV who were asymptomatic, or those who were symptomatic but yet to

experience their first AIDS-defining illness. The children and adolescents represented approximately 2% of all people with AIDS in the USA. A further 20% of people with AIDS were aged 20-29 years and they were most likely to have been infected during adolescence by the sexual or drug-abuse routes.

Most cases were concentrated in the eastern one third of the US, with most cases in urban areas. African American and Hispanic minority groups accounted for more than 80% of the total number of under 19s with AIDS. [Wolters *et al*, 1999]

US haemophiliacs

For the USA Kroner *et al* (1994) showed that the first haemophiliacs were infected in 1978, infections peaked in October 1982 and declined (to approx. 4 infections per 100-person-years) by July 1984.

For those with the highest dosages of factor products, the peak period was earlier, occurring in January 1983. Once the rates were adjusted for dosage of factor products and disease severity, the association between age and early sero-conversion disappeared.

The cumulative incidence of infection (Kroner *et al*, 1994) was:
96% for high dose factor concentrate recipients
92% for moderate dose factor concentrate recipients
56% for low dose factor concentrate recipients.

The infection rate for those receiving products derived from a single donor (per dose) had a 16% cumulative incidence of infection (Kroner *et al,* 1994).

Patients with Haemophilia B ("Christmas Disease", Factor IX deficiency) had approximately half the risk of factor VIII recipients. This difference probably resulted from differing manufacturing processes for the two factors and the smaller number of donor exposures per patient (Goedert *et al,* 1989).

Klein (1998) reported that the transmission rate for recipients given an infected unit of blood was 90% - 95%. During the 1983 -1985 period the risk of contracting AIDS from the transfusion of blood and blood components was estimated at one infection per million units (Klein, 1998). However studies indicate that (in at least some areas) the risk was actually much higher: Minamoto *et al* (1988) calculated the risk for recipients in the San Francisco area from the first appearance of the virus in 1978 to its peak risk of 1.1% per unit in 1983. Busch et al (1991) undertook a retrospective study in New York City which revealed an overall risk which ranged from 0.02 – 0.11% per component transfused. There was positive outcome (Ward *et al,* 1988): donor education, self-deferral and confidential exclusion proved very effective in reducing risk of transmission: by 1984 (before the introduction of antibody screening) the transmission risk had dropped to less than 0.2% per unit.

Europe:

In Europe: homosexual activity and IV drug use were the prevailing transmission routes in all Western European countries, though the Northern European countries tended more to homosexual transmission and the Southern European countries tended more to transmission associated with IV drug use (and associated heterosexual and vertical transmission).

By 1996 (WHO European region data cited by Blanche & Tovo, 1998) the prevalence rates for AIDS in Western European countries ranged from 10 to 180 per million population. The Eastern European region appeared less affected, with less than 0.5 AIDS cases per million population.

Cumulative Paediatric[8] AIDS cases amounted to 6684[9] in Europe in March 1997 (WHO European region data, cited by Blanche & Tovo, 1998). Three countries had the bulk of these paediatric cases: Romania accounted for the majority, n = 4109, with Spain next at n = 816 and France n = 677.

In March 1997 (European Centre for the Epidemiological Monitoring of AIDS, St. Maurice, France cited by Blanche & Tovo, 1998) the UK had 270 paediatric AIDS cases, of whom only 34 were identified as resulting from transfusion or haemophilia. A breakdown of the infection route for the UK paediatric cases (from Blanche & Tovo, 1998, Table 2.4) is provided below in Table 1.3.1.7.2.

[8] CDC definition of paediatric cases = all children under 13 years.
[9] This total is obtained from a total of the cases cited in Blanche & Tovo's Table 2.4, it is different from the figure (n = 2900) they cite in their text at the top of page 16, which appears to be an error.

However Blanche & Tovo (1998, p.15) also noted that the number of AIDS cases is not an especially good indicator of the spread of the epidemic, the estimated prevalence of HIV infection in the general population is a better indicator. For 1996 the UK estimate of prevalence of HIV infection was 7.1 per 10,000 population. See Table 1.3.7.1.1 below for comparisons with other countries.

Table 1.3.1.7.1:

1996 HIV prevalence rates estimated for a range of European regions

(the western European regions have been selected here).

Bernard, Zellweger *et al (1996)*

Region (alphabetical order)	**Estimated prevalence rate per 10,000 population**
Austria	16.1
Belgium	16.3
Denmark	12.3
Finland	1.5
France	25.7
Germany	8.3
Greece	7.87
Ireland	8.0
Italy	24.9
Netherlands	7.1
Norway	4.7
Portugal	13.2
Spain	**48.3**
Sweden	5.8
Switzerland	26.5
Turkey	0.1
UK	7.1

Bold = highest prevalence

Table 1.3.1.7,2 UK paediatric HIV cases by infection route

March 1997 statistics (reported in Blanche & Tovo, 1998)

UK total paediatric AIDS cases:	**Total N = 270**
Total by Vertical transmission:	233
Related to IVDU:	16 (7%)
"High endemic area orig."	166 (71%)
Heterosexual contact:	27 (12%)
Other:	24 (10%)
Haemophilia and transfusion:	34
Nosocomial[10]:	0
Other / not determined:	3

1.3.1.8 Epidemiology of HIV: The current statistics (2001- 2004)

By the end of 2004, there were estimated to be 39.4[11] million people across the world living with HIV / AIDS, including some 2.2[12] million children (aged <15 years). An estimated 4.9[13] million of those people were identified for the first time during 2004. An estimated 3.1 million[14] people, including 510,000 children, died from AIDS during 2004. It is estimated that among the regions, Sub-Saharan Africa had the greatest number of those deaths: 2.3 million [UNAIDS, 2004].

Table 1.3.1.8.1 (below) features a comparison of the 1988 versus 2004 worldwide AIDS statistics for the various regions of the world. There have been changes in that period in the ways in which cases are grouped by region and therefore interpretation can be difficult for those groups. However the worldwide trend is utterly clear: less than half a million cases in 1988; more than seven million cases in 1998 and almost forty million cases in 2004.

[10] Infection acquired in hospital.
[11] Range: 35.9M – 44.3M
[12] Range: 2.0M – 2.6M
[13] Range: 4.3M – 6.4M

Table 1.3.1.8.1: Comparison of 1988 versus 2004 worldwide AIDS statistics

From: WHO AIDS data by region, February 1988 Adapted from Kaslow & Francis (1989b)

Plus: Regional HIV and AIDS statistics and features, end of 2004

(Source: http://www.unaids.org/en/resources/epidemiology/epicore.asp)

Area	Number of AIDS cases Reported at Feb 1988		Number of people living with HIV / AIDS reported at end of 2004	Number of new infections reported at end of 2004	Number of deaths due to AIDS reported at end of 2004
The Americas	60,409 including 53,069 in the USA		Latin America: 1,700,000 Caribbean: 440,000 North America: 1,000,000	Latin America: 240,000 Caribbean: 53,000 North America: 44,000	Latin America: 95,000 Caribbean: 36,000 North America: 16,000
Africa	9,760 largest cohort 2,369 in Uganda, seven countries reported more than 500 cases.		Sub-saharan Africa: 25,400,000 North Africa and Middle East: 540,000	Sub-saharan Africa: 3,100,000 North Africa and Middle East: 92,000	Sub-saharan Africa: 2,300,000 North Africa and Middle East: 28,000

Table 1.3.1.8.1 continued: Comparison of 1988 versus 2004 worldwide AIDS statistics

Area	Number of AIDS cases Reported at Feb 1988		Number of people living with HIV / AIDS reported at end of 2004	Number of new infections reported at end of 2004	Number of deaths due to AIDS reported at end of 2004
Eastern Mediterr-anean	82		This category was not included in the 2004 statistics – appears to have been included in either Eastern Europe or Western and Central Europe.		
Europe	10,245 UK then had 1,227 cases; five European countries reported more than 500 cases.		Western & Central Europe: 610,000	Western & Central Europe: 21,000	Western & Central Europe: 6,500
Eastern Europe & Central Asia	This category was not included in the 1988 statistics		1,400,000	210,000	60,000
South-east Asia	24		South and South East Asia: 7,100,000	South and South East Asia: 890,000	South and South East Asia: 490,000
East Asia	This category was not included in the 1988 statistics		1,100,000	290,000	51,000
Western Pacific	913 largest cohort, Australia: 758 cases		Oceania: 35,000	Oceania: 5,000	Oceania: 700
Total – world	**81,433**		**39,400,000**	**4,900,000**	**3,100,000**

The HIV prevalence among adults was estimated at 1.1% worldwide - though this statistic is potentially misleading, as only Sub-Saharan Africa (7.4%) and the Caribbean (2.3%) have adult prevalence rates above 1%. The other regions have adult prevalence rates which range between 0.1% in East Asia and 0.8% in Eastern Europe & Central Asia [UNAIDS, 2004].

Of the estimated 14,000 people newly infected each day during 2004:

- Almost 2000 per day were children (<15 years of age).
- Approx. 12,000 per day were people aged 15 – 49 years and of those
  - approx. 50% were female
  - approx. 50% were aged 15 – 24 years.
- Over 95% occurred in low income or middle income countries.

The WHO (2002) reported that, worldwide, approximately 7000 people aged 10 - 24 years became infected by HIV every day, which was approximately 50% of all new infections, yet early adolescence is considered one of the lowest infection risk periods.

The UNAIDS *"AIDS Epidemic Update December 2002"* provided the following worldwide statistics (each of the statistics from this report is indicated by a bullet point):

- Life expectancy at birth in sub-Saharan Africa was estimated (2001) at 47 years; without AIDS it was estimated at around 62 years.

[14] Range: 2.8M -3.5M

- Estimates suggested that 95% of the HIV infections in Africa were attributable to unsafe sex (i.e. mostly in heterosexuals).

- In the rest of the world the estimated percentage of HIV infections in 2001 that were attributable to unsafe sex ranged from 25% in Eastern Europe to over 90% in parts of South America and the "developed" countries of Western Pacific.

In 2001 3% of deaths in children aged under 5 years were a direct result of HIV infection [WHO, 2001].

Blanche & Tovo (1998) reported that the estimated prevalence of HIV infection in the general population is a better indicator of the extent of the epidemic than the number of cases who have reached the AIDS stage. Table 1.3.2 is a summary of the 1996 prevalence rates estimated for a range of European regions.

The People's Republic of China

A report in the *Shanghai Daily* [15] (19 Feb 2004, p. 4) derived from a report by the Chinese Ministry for Health indicated that HIV infection is prevalent in all areas of China. The report indicated that China has 840,000 people with HIV infection, of whom 80,000 have progressed to AIDS. It noted that whilst currently most HIV infected people were infected by blood transfusions,

[15] The newspaper report collected during travel in China.

sexual transmissions increased from 5.5% in 1997 to 10.9% in 2002. The newspaper report quoted Dai Zhicheng, vice-chair of the China Sexually-Transmitted Disesases and AIDS Prevention and Control Association saying

> *"the virus is epidemic, not only among high-risk groups such as drug-users and sex workers, but also among the general population".*
>
> [*Shanghai Daily* [16] 19 Feb 2004, p. 4]

The Ministry of Health Report went on to warn that China can expect more than 10 Million of her people to be HIV positive by 2010, unless effective counter-measures are put in place.

The United Kingdom

The UK Health Protection Agency Communicable Disease Report (UK HPA CDR, April 2003) produced the following statistics for infections diagnosed up to the end of 2002:

- n = 5338 people were first diagnosed with HIV infection during 2002.
- The highest new infection rates were (as in previous years) in London and the South East of England.
- London has 60% of all cases in the UK.
- Heterosexual transmission (54%, n = 2899) was the most common route (4th continuous year).

[16] The newspaper report collected during travel in China.

- 28% (n = 1481) of infections were acquired by male-male sexual transmission.

- 2% (n = 84) of infections occurred through injecting drug use (IDU).

- Where ethnicity was reported (68% of reports), just over half of new cases in 2002 were among people of black African origin. It was reported to be probable that 71% of those people were infected while in Africa.

Since UK recording began, in 1982:

- a total of 56,108[17] people have been reported as having been infected with the HIV.

- 35% (n = 19,166) of those diagnosed with HIV infection have (so far) gone on to be diagnosed with an AIDS-defining condition.

- 65% (n = 12,544) of those with AIDS have subsequently died.

- a further 4.5% of the total number infected (n = 2455) have died without having been reported to have developed AIDS.

[17] This web source has slightly contradictory information: a few pages later under the heading "AIDS and HIV infection in the United Kingdom: monthly report January 2003" the cumulative total since 1982 was given as 54,261. The discrepancy probably results from delays in monthly reporting and hence the belated inclusion of earlier diagnoses into later reports.

Table 1.3.1.8.2

UK Health Protection Agency Communicable Disease Report (UK HPA CDR, April 2003.

Source: http://www.hpa.org.uk/cdr/archive03/hiv03.htm

Reproduced from their "Table 1 HIV infected individuals by year of diagnosis: UK data to end of March 2003"

Probable route of infection	1992 or earlier	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002†	Total‡
Sex between men*	14,422	1497	1483	1465	1544	1400	1352	1340	1488	1676	1481	**29,322**
Sex between men and women	3035	767	796	850	836	1009	1158	1424	1981	2826	2899	**17,870**
Injecting drug use	2492	205	167	183	172	167	130	112	108	127	84	**3954**
Blood Factor	***1337***	***4***	***2***	–	***2***	***2***	***2***	***1***	***1***	***2***	***3***	***1356***
Blood / tissue transfer	184	13	15	20	18	25	8	18	22	23	19	**366**
Mother to infant (vertical)	176	66	64	61	62	79	93	81	100	81	96	**973**
Other / Undetermined	580	63	49	66	57	51	67	82	120	237	756	**2267**
Total	**22,226**	**2615**	**2576**	**2645**	**2691**	**2733**	**2810**	**3058**	**3820**	**4972**	**5338**	**56,108**

* includes 698 individuals who also injected drugs † numbers will rise as further reports are received ‡ includes 624 cases diagnosed in 2003

- 22% (n = 11,600) of those infected by the HIV were women; of whom 24% (n = 2733) had developed AIDS; and 15% (n = 1698) had died.

- A disproportional number of women have become infected in recent years. The number of HIV positive women started to increase slowly from 1993, this number escalated significantly from 1999. Between 2000 and 2001 there was a 48% increase in women infected, a similar increase was expected in subsequent years.

- 1356 of the total UK cases (2.42%) were people who acquired their infection by the "blood factor" route.

[UK HPA CDR, April 2003].

1.3.2.1 The natural history of HIV infection

The HIV has a particular affinity for the CD4 surface receptor sites on "helper T cells" (CD4 lymphocytes), (Klimas, 2000). It can also infect cells which derive from bone marrow lineage, including the long-lived monocytes and blood-derived macrophages of the immune system, and the intrinsic microglial cells (forming the connective tissue and resident mononuclear phagocytic system of the brain) which have CD4 receptors (Belman, 1997). Multi-nucleated giant cells may be formed from the fusion of these cell types (productive infection). Endothelial cell infection has also been reported, though this is not a consistent finding (Belman, 1997). These cells can act as

viral reservoirs. (See also footnote 1). The virus's infection of key cells in the immune system make this infection difficult for the body to fight.

Tests for the HIV-antibody (March 1985, test is called "ELISA") and later viral culture tests were introduced, making it possible to estimate the extent of the infection in the various risk groups for the first time.

Haemophiliac patients' risk of HIV infection prior to 1986 was related to the frequency of Factor VIII or Factor IX treatment and hence to the severity of their haemophilia. In the UK 25% of the mild group, 45% of the moderate group and 75% of the severe group having become infected (Eyster, 1991).

The United States (US) Centre for Disease Control (CDC) developed a disease classification system for HIV / AIDS which became the international standard descriptive system (CDC, 1987, revised 1992 and 1997). See Table 1.3.2.1 for a summary table.

The original CDC classification, which was still in use at the time of the current study identified four stages of HIV infection, labelled with Roman numerals, with stage IV (colloquially known as *"full blown AIDS"*) being sub-divided according to the types of opportunistic infection or other symptoms experienced.

The International Classification of Diseases (ICD, 1992) also provides a classification system for HIV infection, but it was not used in the current study.

Riccio *et al* (1989) commented that HIV encephalopathy (i.e. the physiological damage attributed to the *direct* action of HIV within the CNS*) "appears to have its direct clinical correlate in the AIDS Dementia Complex [ADC]"* (p.1). They added that little was known about the natural history and rate of progression of HIV associated neuropsychiatric disorder. McArthur (1989) suggested a "liberal estimate" that 60% of AIDS patients might develop a dementia at some point in their illness. Clinical evidence suggested that the most severe forms of HIV associated dementia typically occurred in those with the most advanced forms of HIV disease and that the onset of dementia indicated a poor prognosis.

Riccio *et al* (1989) also commented that *sub-clinical* neuro-psychological abnormalities had been reported in some studies, ranging from 0% in the Multicentre AIDS Cohort Study (1988) to 44% in Grant *et al* (1988).

The frequency of occurrence of a particular white blood cell (T4 or CD4 lymphocyte) called the "CD4 count" for an infected individual's blood is considered a marker for the degree of immune suppression. This marker is also a reasonable indicator of disease progression, at least where no measure of viral load is available, and so it is incorporated into the latest CDC classification system for HIV disease. The CD4 count has therefore been recorded in most studies of HIV infection and will be reported in this study.

In the absence of an antibody test or viral culture, the first strong indication of illness in a person with HIV infection is often the onset of an opportunistic infection. Such infections may be life threatening in themselves, or they may be successfully treated but indicate declining immunological function, and other infections to follow. Typically such opportunistic infections may include: thrush, pneumonias (especially the *pneumocystis carinii* pneumonia [PCP]), cytomegalovirus, etc.

The CDC classification system for the stages of HIV infection was changed again in 1992. The new system emphasised the importance of CD4 count (viral load measures were not usually available at that time). See Table 1.3.2.2 for a comparison of the 1987 and 1992 CDC classification systems for HIV disease.

In general terms the sequence of stages of infection is:

- Primary infection (may be wholly asymptomatic or feature a mild, flu-like illness)
- Asymptomatic phase
- Symptomatic phases – AIDS-related Complex [ARC]
- AIDS

Much of the improvement in life expectancy in recent years comes from better prevention and treatment of the common opportunistic infections (Tuddenham and Laffan, 2001).

Table 1.3.2.2:
Comparison of the 1987 and 1992 CDC classification systems for HIV disease

Old classification		New CDC classification
CDC stage (1986 version)	**Description / important features**	**CDC clinical category (1992 version)**
I	Initial infection	Stages I, II and III become **Clinical Category A –** asymptomatic HIV infection; persistent generalised lymphadenopathy (PGL); acute (primary) HIV illness A1 = CD4 > 500/μl A2 = CD4 of 500 to 200/μl A3 = CD4 <200/μl
II	Asymptomatic period	
III	Persistent generalised lymphadenopathy [PGL]. The Symptomatic stage – or the AIDS Related Complex (ARC).	
IV a	Other diseases – constitutional disease	Stages IV a, c2 or e become **Clinical Category B** – symptomatic (not A or C conditions) . Examples include vaginal candidiasis persisting more than one month and responding poorly to treatment; Oropharyngeal cervical dysplasia (severe or carcinoma *in situ*); constitutional symptoms such as persistent fever or diarrhea lasting more than one month. B1 = CD4 > 500/μl B2 = CD4 of 500 to 200/μl B3 = CD4 <200/μl **Clinical Category C** – HIV wasting syndrome or various opportunistic infections inlcuding: candidiasis affecting the oesophagus, trachea, bronchi; Extra-pulomonary coccidioimycosis, or cryptococcosis, or M. avium, or M. Kansaii; Invasive cervical cancer; Chronic (longer than one month) intestinal cryptosporidiosis; Bronchitis, pneumonia; Diseminated extra-pulmonary histoplasmosis; Chronic (> 1 month) isosporiasis; Kaposi's sarcoma; Lymphoma (Burkitt's, immunoblastic or primary in brain); M. tuberculosis (pulmonary or extra-pulmonary); Pneumocystis carinii pneumonia; Recurrent pneumonia (>2 episodes per annum); Progressive multi-focal leukoencephalopathy; Recurrent Salmonella bacteremia; Cerebral toxoplasmosis. C1 = CD4 > 500/μl C2 = CD4 of 500 to 200/μl C3 = CD4 <200/μl
IV b	Other diseases – neurologic disease	
IV c1	Other diseases – specified secondary infectious diseases [includes PCP, CMV and progressive multi-focal leukoencephalopathy, candidiasis (except oral)]	
IV c2 (NB: only IV c1 diseases were included in the definition of AIDS]	Other diseases – other specified secondary infections [includes tuberculosis and oral candidiasis].	
IV d	Other diseases – secondary cancers	
IV e	Other diseases – other conditions	

Table composed from CDC, 1987 and 1992 plus Kilmas (2000) Table 1.2 (page 12)

1.3.2.2 The natural history of HIV infection in children:

Belman (1997) noted that the natural history of vertically acquired HIV infection differs from that of those who acquire their infection as adults. The adverse effects of HIV-1 on the nervous and immune systems as they develop frequently results in a more rapid onset of symptoms and more rapid disease progression.

Belman (1997, p. 225) described a *"bimodal evolution of pediatric HIV-1 disease"* with the clusters of cases occurring in infancy ("first group") and in later childhood ("second group"). Belman added that the model may in fact be "tri-modal" since there is a smaller third cluster ("third group") in the pre-adolescence and early adolescent years. She also noted that the latency period (from infection to first onset of symptoms) may be 10 years or more for those who are in the third group, which is similar to the adult latency period.

Among Belman's "first group" cases the CDC AIDS surveillance reports showed that 62% had PCP as their first indicator disease, compared with only 20% of infants diagnosed before one year of age. Children in the "second group" typically displayed a more "indolent" course, with Lymphoid Interstitial Pneumonia (LIP) as their most frequent indicator disease. LIP has a much better survival prognosis than PCP. They also tended to have evidence of other lympho-proliferative processes characteristic of childhood HIV disease, including lymphadenopathy, hepatosplenomegaly and parotid gland enlargement.

Belman (1997, p. 225) commented:

"Data modelling of the CDC's Pediatric Spectrum of Disease Study also supports the clinical impression of two distinct populations of children with different rates of survival. Analysis showed that the difference between groups was not related to any difference in PCP prophylaxis, specific AIDS-defining conditions, antiviral therapy or birth weight. [Byers et al, 1993; Oxtoby, 1994]".

Belman (1997) also commented on the natural history of HIV infection in adolescents (13-19 years): this age group comprised approx. 1% of all AIDS cases in the USA in March 1993. Other statistics indicate that approx. 20% of AIDS cases are in the 13-29 year age group. Given the ten year latency period, Belman argued that most of those in the 20-29 age group were probably infected as adolescents. Early in the history of HIV infection the teenage cases typically resulted from iatrogenic infection, but more recently (thanks to anti-viral heat treatment of products) the most common risk factors for adolescents have become sexual exposure and IV drug use. Belman suggested that approx. 65% of adolescents were infected by these means and the number of cases continues to increase steadily.

Belman (1997) suggested that children with HIV are now living longer, this is in part due to earlier and more accurate identification and diagnosis but also is due to improved prophylactic therapy, more effective treatment of infections and anti-retroviral therapies. She added (Belman, 1997, p. 226):

"Pediatric HIV-1 infection can now be thought of as a chronic dissease, with multi-system involvement, that [has] *periods of progression and periods of relative stability."*

1.3.2.3 The phases of HIV disease progression

(groupings derived from the 1992 revision of the CDC classification system)

1.3.2.3.1 Primary infection (CDC Category A)

On entry to the host's cells viral replication can commence and rapid replication can result in a viral load of millions of virions per 1cc of blood within the first few weeks of infection. The virions are present in high densities in all of the lymph nodes and in lymphatic tissue. During this acute infection phase patients often experience an influenza-like illness (Kaslow & Francis, 1998 mentioned that it resembles the syndrome of acute infectious mononucleosis). Patients may also have a rash, plus an illness known as Acute Retroviral Syndrome, which may onset 1-6 weeks from infection with a range of non-specific symptoms from fever, sweating, myalgia, nausea, diarrhoea and sore throat. Blood tests reveal reduced lymphocyte count, elevated sedimentation rate and elevated liver enzymes. [Klimas, 2000]

Generalised lymphadenopathy (GL) is described by Kaslow & Francis (1998, p.109) as the *"most consistent clinical feature of the early infection"* and may appear even before antibodies are detectable (Polis *et al,* 1988). Kaslow & Francis (1998, p. 109) speculate that more than half of homosexual men, and

probably other groups too, develop GL within one year of sero-conversion, though showing this sign, or not, is not a predictor of disease progression.

During this acute phase the patient is losing CD4 cells (a drop of 40% is common) resulting either from direct cell lysis, immunological destruction of affected cells, or redistribution of cells to the lymph nodes and lymphatic tissues. The CD8 count initially drops, but then rises. HIV viremia can be detected (directly) within days, antibody tests are not positive for at least two weeks. [Klimas, 2000]

As the immune system attempts to cope with the infection the CD4 count typically rebounds to 80-90% of normal and an elevation of the CD8 count reflects a vigorous anti-viral response. The IgG antibody should appear approximately 3 weeks post-infection and is reliably present by 3 months. [Klimas, 2000]

Within 2-3 months of exposure, in most people[18], antibodies to the viral envelope and core proteins are detectable, signifying that infection is established (Kaslow & Francis, 1998). In an unknown proportion of those infected, core (p24 or p55) antigen may be detectable a few weeks before antibodies appear.

Kaslow & Francis (1998) identified a number of factors which may modify the risk of infection (or the risk of progression to symptomatic disease):

[18] Kaslow & Price (1998) discussed a sub-group of infected people who either appear not to develop the antibody, or who develop it and then "lose" it again later.

1. **Mechanical trauma:** the mechanical effects of mucosal disruption may facilitate penetration by HIV-1 (this has also been found for Hepatitis B). hence use of a douche or enema prior to anal intercourse actually *increases* the risk of infection by traumatising the ano-rectal tissues. Other studies have shown that menstruation increases the risk of HIV infection (again this is similar to other sexually transmitted infections). However, Fultz et al, (1986) demonstrated with a single case (chimpanzee) that neither trauma nor menstruation was necessary to produce infection by the vaginal route. It is possible that trauma facilitates infection, either by enhancing contact between virus and target cells in the intestinal or genital tract; or simply by stimulating T-helper cell activation.

2. **Co-infection**: there are at least two plausible mechanisms by which co-infections may increase the risk of HIV infection.

   (i) Some other infections produce ulcerative or inflammatory responses. These resemble tissue responses to physical trauma and therefore may provide a similar route for the virus.

   (ii) the inflammatory response to the co-infection may be bring effects in the immune system which are essential (or just helpful) to the initiation of HIV-1 infection.

3. **Chemicals / Drugs**: use of the major psycho-active drugs has been shown to be associated with higher risk of infection (Ostrow *et al*, 1987;

Stevens *et al,* 1987), probably because their use is associated with higher risk sexual practices.

Progression rates: Research has identified some sub-groups of HIV positive patients who have slow disease progression and much interest has centred on identifying which factors inhibit disease progression. The initial immune response is important in determining the progression rate thereafter: the strength and diversity of initial response help to clear the initial viral load and this level becomes the "set point" of viral load. Patients with a high set point have a rapid disease course. [Klimas, 2000]

Certain factors may influence the set point of viral load during primary infection (see below):

1. **Lower viral inoculum**: it seems obvious that those infected with a large quantity of virus (e.g. a large volume of contaminated blood) are more likely to get a rapid viral expansion before the immune system can respond and hence infection is more likely. [Klimas, 2000]

2. **Viral strain and tropism:** longer-term survivors tend to harbour the less virulent strains of the virus (e.g. those which infect macrophages and reproduce poorly in CD4 cells). However a normal immune response is required to manage even the less virulent strains of the virus. [Klimas, 2000]

3. **Efficiency and type of host immune response**: an immune response which favours cytotoxic T cells is more effective against the HIV than a response which favours the B cells or antibody production. In addition long-term survivors tend to have present an antibody which neutralises and often inactivates the viral particles (whereas some other have antibodies which are either ineffective or sometimes enhance viral entry into cells). Long-term survivors are characterised by an early and brisk CD8 response which is effective, precedes seroconversion and results in a low viral load during the latency period. In addition to this, "survivors" tend to have better "natural killer" cell (NK) function than "progressors", (Solomon *et al,* 1994) and this may be important since NK cell functioning has been linked to psychological factors such as stress and coping. In particular, high levels of the "stress" hormones cortisol, adrenaline and nor-adrenaline may be accompanied by decrements in immune function. [Klimas, 2000]

4. **Susceptibility of host cell to infection**: approximately 50% of "survivors" have a genetic trait which helps to protect the CD4 cell from viral entry: the T cell receptor has a sugar molecule effectively blocking the CD4 receptor, preventing the attachment of the HIV.

1.3.2.3.2 Asymptomatic HIV infection

(CDC 1992 Category A, previously Stage II)

Generalised lymphadenopathy is the most consistent clinical symptom of early infection, sometimes this occurs before the antibody is detectable (Polis *et al,* 1988).

Klimas (2000) noted that following initial infection and the initial immune response, the viral "set point" stabilises and there is an asymptomatic interval which may last months to years. Without anti-viral treatment this interval averages 10-12 years.

One explanation for the HIV's persistence, despite a powerful immune response, is its mutation rate. Typically an asymptomatic person might have a total viral load of 10^{12} with a turnover of 10^{10} virions per day (Ho, 1997). At this rate of reproduction one could expect a random mutation to occur approximately every four hours. Those mutations which prove more resistant to the host's immune response will be more likely to survive and reproduce (by a process of natural selection) and so the virus becomes more **resistant** over time to the immune response. There are two other means by which the virus negates the immune system: direct killing of the CD4 cells which would usually orchestrate the immune response to virus-infected cells and polyclonal activation leading to apoptosis (programmed cell death) of both CD4 and CD8 cells.

The primary clinical finding in the asymptomatic phase is persistent generalised lymphadenopathy (PGL), further categorisation under the CDC 1992 criteria is according to CD4 count (see Table **CCVVV).**

The rate of progression to symptomatic stages is highly variable: about 9% of people have a stable high CD4 count 10 years post-infection, but 10% of people with HIV die in the early years of their infection (Klimas, 2000). The median time from infection to an AIDS-defining illness was 10 - 12 years at the time of this study (Levy, 1993).

Factors influencing the rate of progression to Clinical Category C include:

1. **Co-infection**. Klimas (2000) notes that those with concurrent tuberculosis, hepatitis B or C or herpes simplex progress more rapidly than those without active co-infection. This may relate to T cell activation which affects viral replication rates. Viral co-infections may also accelerate HIV replication by sharing viral genes (Laurence, 1990; Nelson *et al*, 1988)

2. **Genetics**. As mentioned previously, some individuals have a genetic trait which partially blocks HIV attachment to the CD4 receptor.

3. **Age.** Older individuals with HIV have a faster progression rate than younger adults, possibly because as we age there are fewer naïve immune cells and more "memory" CD4 cells, which are the virus's

preferred target. So these CD4 cells may be depleted more rapidly, or possibly the bone marrow, thymus and extra-thymic factors are less able to sustain the cell loss in the older person. (Becherer *et al*, 1990)

4. **Viral strain.** As previously noted, some strains are more virulent than others. The most virulent cause CD4 cells to fuse together with multiple nuclei, producing enormous quantities of virions without immediately killing the host cells. (Klimas, 2000).

5. **Behaviour.** Patient mood and coping style have repeatedly been shown to influence disease progression, even before effective anti-viral treatments were introduced. To summarise: optimism, better sense of personal control and not being depressed are all associated with slower disease progression. (Klimas, 2000). With the introduction of effective but complicated medication regimes, these factors interact with mood and coping to influence treatment adherence – and good adherence has a considerable effect on efficacy of treatment and longevity. Several studies have shown that treatment adherence is poor (Deeks and Volberding 1998; Klimas, 1998; Kastrissios *et al*, 1998) and may be as low as 50%, even among those doctors thought were compliant, which translates into multiply drug resistant HIV strains and rapid disease progression. Klimas concluded:

"These data would suggest that half of the patients whose physicians judged them to be compliant and had proved to be resistant to all

available regimens still did not take enough medication to develop resistance or a clinical response." Klimas, 2000, p.19.

6. **Sex.** One series of students (Scott *et al*, 1985) indicated that pregnant women may show rapid progression of HIV-1 infection. Though this finding has not been systematically researched in a large population, (natural and experimental) variations in sex hormones are known to be associated with significant changes in immune response (Kaslow & Francis, 1998).

3.2.3.3 Effects reported during CDC Clinical Category B (stages III - IV of HIV infection) - symptomatic phase and AIDS

The chronic phase of illness (Category B – sometimes known as the ARC – AIDS-related Complex) is characterised by symptoms, other than PGL, which are not severe enough to be AIDS-defining but which suggest progressive immunosuppression and a constitutional illness. The symptoms most frequently include:

◊ Fatigue

◊ Fever

◊ Diahorrea and / or weight loss

◊ Myalgia

◊ Night sweats

◊ Weight loss

◊ Oral candidiasis

◊ Recurrent vaginal candidiasis

◊ Oral hairy leukoplakia

◊ Skin conditions such as flat warts, psoriasis, atopic dermatitis, seborrhoeic dermatitis, folliculitis

[Tuddenham and Laffan, 2001].

The evidence of neurological involvement in Category B is reviewed in Introduction Section 4.

3.2.3.4 Effects reported during CDC Clinical Category C (stages III - IV of HIV infection) - AIDS

Kaslow & Francis (1998) noted that estimates of the *incidence* of AIDS (i.e. what proportion of those who are HIV positive will develop AIDS within a certain timeframe) are limited in various ways. These limitations include sample size and selection method. It may turn out that the incidence curve will alter according to person, place or time but such research has yet to be undertaken. They noted that the most reliable estimates, from larger scale studies, suggest that 35-45% of sero-positives will develop AIDS by eight years after infection. Therefore the pessimism about the outcome of infection should be balanced by the fact that most infected people can expect to "live with HIV" for nearly a decade before they develop AIDS, even without effective treatments.

Although the formal CDC classification system allows sub-division of category C (stage III – IV) according to the CD4 count, as in the other categories, most adults will present with an AIDS-defining illness once the CD4 count falls

below 200 cells /mm^3, this level being approx. 25% of the average CD4 count for a healthy person, Evans *et al*, 2000).

The most common opportunistic infections in those with immunosuppression who are not taking preventative medication are:

- Pneumocystis carinii pneumonia [PCP]
- Oesophageal candidiasis
- Cerebral toxoplasmosis
- Mycobacterium tuberculosis
- The wasting syndrome (unintentional weight loss >10% of body weight).

As the CD4 counts nears zero the following often occur:

- Cytomegalovirus [CMV] retinitis
- Mycobacterium avium complex
- Progressive multi-focal leukoencephalopathy
- Lymphoma
- Aggressive cervical carcinoma

The evidence of neurological involvement in Category C is reviewed in Introduction Section 4.

AIDS therapies focus on clearing any current infection, then prevention of recurrence through prophylaxis. Anti-retroviral drugs may restore some of the lost immunological response, helping to prevent further infections.

The development of a detailed understanding of the virus, immune system responses and of responses to certain drug actions has made it possible for researchers to develop highly tailored pharmacological anti-retroviral treatments which have some efficacy when used in the proper, complex, regimes. However these drugs are expensive, adherence is poor and the treatments are simply not available in the worst affected parts of the world.

Therefore the prevention of HIV infection remains the most effective method of curtailing this epidemic. Vaccine development is making very slow progress due to the exceedingly fast mutation of the virus.

See Appendix 7 (Immune System) for a detailed description of the effects of HIV infection on the Immune System.

The evidence concerning the various neurological and neuropsychological effects of HIV is described in more detail in Introduction Section 4. To summarise briefly:

"Convergent neurologic, pathologic and neurodevelopmental data support the hypothesis that dementia in adults, developmental regression in infants, and a clinical picture of progressive encephalopathy in young children may be the consequences of direct or indirect central nervous system effects of infection with human immunodeficiency virus". [Whitt *et al* (1993, p.52)]

1.3.3: HIV and children

Most children (approx. 90%) infected by HIV acquired their infection vertically, from their mother during pregnancy or birth (CDC, 1995). The parents are typically IV drug users or sexual partners of drug users. A relatively small proportion of paediatric cases result from infected blood products.

The CDC paediatric HIV classification (1994) for children under 13 years is presented in Table 1.3.3 below (source: Belman, 1997, Table 2).

Paediatric AIDS is characterised by frequent CNS involvement which adds significantly to the morbidity of the disease. This neurological dysfunction usually cannot be accounted for by opportunistic infections, neoplasms or CVA (Smith *et al*, 1997). There is wide variation in the nature and severity of the symptoms of paediatric HIV disease (Sirois *et al*, 1998). The neuropsychological effects of HIV infection in childhood are discussed in more detail in Introduction Section 4.

One reason why children not infected by the vertical route are of particular interest is because they may have fewer of the potentially confounding environmental variables (e.g. parental drug / alcohol use during gestation resulting in neurological deficits). This may allow researchers to get a clearer picture of the effects of the virus, uncomplicated by other factors.

Table 1.3.3 The CDC paediatric HIV classification (1994) for children under 13 years (source: Belman, 1997, Table 2).

Immunological categories	Clinical categories			
	No signs / symptoms	Mild signs / symptoms (A)	Moderate signs / symptoms (B)	Severe signs / symptoms (C)
No evidence of suppression	N1	A1	B1	C1
Evidence of moderate suppression	N2	A2	B2	C2
Severe suppression	N3	A3	B3	C3

Another possibility for factors complicating the interpretation of research findings is that "children" do not form a homogenous group. This was not recognised in the earliest studies, where children of all ages and those with vertical and other transmission vectors were grouped together. Part of the reason for the variation in findings from various groups studying children with HIV infection probably comes from the differing ages at which those children were infected. It appears likely that, as the brain is a major target of HIV, we will see differences between those infected vertically, those infected in the neonatal period and those infected during infancy or childhood.

Cohen *et al* (1991) studied premature children infected in the neonatal period by blood transfusion. At assessment they were 3-9 years old and were matched with HIV negative controls of similar birth and transfusion history. When tested on two occasions with an eight month interval Cohen *et al* found that these children showed slight but statistically significant differences on motor speed, visual scanning, cognitive flexibility, reading and arithmetic which worsened over time. Though the deficits identified were described as similar to those seen in adults with HIV infection, the confounding variable of

premature birth makes these results difficult to interpret. Premature infants are at higher risk for developing cognitive deficits (Janowsky and Nass, 1987; Washington *et al*, 1986) and it is possible that this risk interacts with the effects of HIV to produce a different outcome to that observed in full term HIV infected children (Smith *et al*, 1997).

1.3.4 HIV and haemophilia

Klein (1998, p. 110) commented:

"Transfusion recipients may be the most valuable group for studying disease progression, because the date of infection is known, and many blood recipients have only a single exposure and lack other potential risk factors."

HIV has similar effects in people with haemophilia as it has in others. There is one form of infection which seems to be unique to the haemophiliac population: infection of a major joint (septic arthritis) which has symptoms which resemble haemarthrosis, but the swelling and pain does not respond to blood product treatment. Septic arthritis is more common in joints which have been replaced by artificial joints. (Jones, 1995)

Heat treatment of blood products in the United Kingdom (UK) was introduced in 1984 (Jones, 1995). This effective virucidal treatment of all blood and products virtually prevented the accumulation of new cases by this vector (Williams *et al*, 1990). The cohort of haemophiliacs in this study are believed to have been infected between 1970 – 1985.

The Haemophiliac population differs from other "at risk" groups in a number of ways: in particular because, unlike most other groups, HIV infection ("*seroconversion*") has occurred across the full age range from infancy to late adulthood. Also, though there are some complications of haemophilia, research with this population can permit the study of the neurological effects of HIV in patients who are less likely to have a history of personal or maternal drug use. This population can therefore represent an opportunity to investigate the effects of the virus without such potentially confounding variables.

Some studies suggest that the incubation period for HIV in people infected through blood products may be longer than for those infected vertically:

- Epstein *et al* (1988) reported a range (for development of AIDS symptoms) from 2 months to 5 years for infections acquired *in utero.*

Whereas:

- Curran *et al* (1988) reported a mean interval of 2 years for those aged under 5 years when infected by blood products and a mean interval of 8 years for those aged over 5 years when infected iatrogenically.

- One study, by Eyster (1991) reported mean incubation intervals as long as 18 years for some individuals who were infected by transfusion.

- Calculations based on US surveillance data (Wilson & Holmes, 1991) in a sample of n = 3518 indicated that the mean incubation period for TA-AIDS[19] was estimated at 18 years.

Studies of haemophiliacs have indicated that the age of the patient at sero-conversion is associated with the length of the asymptomatic interval[20]. At seven years post-infection:

6% of those aged under 25 years were symptomatic;

20% of those aged 25-44 years;

34% of those older than 45 years.

(Lee *et al*, 1989; Lee *et al* , 1991; Darby *et al* , 1990).

Goedert *et al* (1989) and Eyster *et al* (1987) demonstrated that older age was associated with a greater incidence of AIDS in haemophiliacs. They also reported that clinical AIDS was rare in the first two years after infection, but that by the time 8 years had elapsed the cumulative rate for adults was four times greater than that for children or adolescents.

A report from UK Haemophilia Centres (Darby *et al,* 1989) showed that for 1200 people infected with HIV, the incidence of AIDS at five years elapsed after infection was:

4% for those under 25 years.

[19] TA-AIDS is transfusion-acquired AIDS.
[20] the period between acute infection and the first appearance of symptoms of AIDS is the asymptomatic interval.

6% in those aged 25-44 years.

19% among those older than 45 years.

A multi-centre cohort study (Goedert *et al,* 1989) of haemophiliacs produced an AIDS incidence rate of 2.67/100 person-years and this rate was directly related to age.

A similar relationship to age is found in tranfusion associated AIDS cases: Lagakos & De Gruttola (1989) reported that n = 844 cases produced a median latency of 6.7 years for the whole sample, compared to 3.7 years for those infected before one year of age. Overall Klein (1998, p. 110) summarised: *"It appears that the interval from the transfusion-acquired infection to the onset of disease is shortest in neonates and older adults, with children & younger adults having longer periods of latency."*

The reasons for the differences in AIDS incidence at different ages are not known, but Klein (1998) speculated that it could be related to the maturation of the immune system.

Haemophiliac children and adolescents have a similar case-to-fatality ratio to other, age-matched, children who have AIDS (Jason *et al,* 1988). In 1990 in the US, boys and young men with haemophilia were the largest group of young people with AIDS (CDC, 1992). However it can be demonstrated that HIV-infected young people have continued to accumulate in the population, either from vertical transmission during gestation or in infancy, or by intra-

venous or sexual transmission in adolescence (Mann, 1990; CDC 1995). It is likely that in future some cases of non-vertical HIV infection will occur in children prior to adolescence e.g. as a result of child abuse (Stolar and Fernandez, 1997). Therefore study of the young Haemophiliacs can provide data concerning the effects of the virus in this age group (i.e. children infected post-infancy but prior to adolescence) which is not usually available from other populations.

In particular there may be differences (compared to adults or people infected during the foetal / infant period) in the effects of the virus on the nervous system of younger people. Brain development in childhood differs qualitatively from other life stages, this being a period of cellular maturation rather than production of new cells and structures e.g. extensive myelination of axons; elimination of unnecessary synaptic links; and development of new synaptic links between cells, all tending to produce increasing organisation. See Introduction Section 4 for a discussion of brain development. Sirois and Hill (1993) note that the effects of HIV in children are less well understood than those in adults, and that many studies include populations which are skewed towards infancy because of the prevalence of vertically infected children. The studies are difficult to interpret because the results have not been organised in respect of particular age groups.

Sirois and Hill (1993) discussed models which might account for the observed pattern of gradual, barely measurable decline in performance during the asymptomatic period. Nadel (1990) reported that many researchers have

observed such gradual decline in both "normally ageing" people and in those with some form of brain disease or injury. Nadel (1990) suggested that the "percolation theory" might explain such regression: there might be little observable change in a person's overt behaviour as particular structural elements of the CNS are damaged, but once the system reaches some "critical threshold of loss", abrupt changes in behaviour may become evident.

Sirois and Hill (1993) argued that HIV disease could fit this "percolation model": the virus may gradually alter neurochemistry and / or brain structure, but the critical threshold does not occur until around the time the physical symptoms meet the CDC category B / C criteria. They argue that their own findings and those of other studies of children with symptomatic disease fit this model. They add that one possibility is that secretion of neurotoxins by infected glial cells (Guilian *et al,* 1990) affects the developing nervous system. This could occur in any of three ways: (a) disruption of neural migration (b) disruption of the synaptogenic process during peak growth spurts and (c) disruption of the process which eliminates excess synapses. They note that this theory appears especially plausible given the observation that a peak period of synaptic change has been identified (Fischer, 1987) in children ages 2-4 years, which coincided with the age at infection of the Sirois and Hill (1993) younger infected group, who displayed greater neurological damage than those infected in later childhood.

Research may determine whether the childhood-infected age group differs from those infected at other stages of their development and will help to

identify the care needs of those infected in childhood and their families. For example: if HIV infection imposes the strain of psychiatric disturbance or cognitive impairment in addition to the stresses consequent on Haemophilia, then both professional and informal carers will need to be aware of this, in order to cope appropriately with those potential problems.

Introduction

Section 4

Neurological and psychological manifestations of HIV infection

1.4.0 Introduction – Section 4
Neurological and Psychological manifestations of HIV infection

1.4.1 The pre-1990 literature

When the present study was planned (1988 - 1989) serious neuro-psychological impairment had already been identified in adults with AIDS [CDC Stage IV (Category C) HIV-related disease]. For example: Navia *et al,*(1986). However it was unclear whether HIV itself, or something indirectly related, such as the various opportunistic infections, was the cause of such symptoms.

In 1990 when the data collection for this study began, there remained controversy over whether patients with asymptomatic HIV infection (stage II-III or category B) could and did have subtle neurological and neuropsychological symptoms which might be earlier indicators of nervous system involvement and might possibly be the pre-cursors of HIV dementia. Some authors (e.g. Grant *et al,*1987) argued that there was evidence of subtle changes in the cognitive function of some patients, others disagreed with this claim and / or were unable to confirm this finding in their samples (e.g. Selnes & McArthur, 1992). The picture was further complicated because of the very high incidence of drug-use and other potentially confounding factors in the histories of many HIV infected people.

In 1998 Kaslow & Francis noted that neuropsychological dysfunction may occur at any point after the HIV infection occurs and the acute symptoms (if any) have subsided. They add that this is *likely* to be later in the course of illness, but acknowledge this may be because the early manifestations are

subtle and therefore may go unnoticed. Even after a number of years of research

> *"neither the precise sequence nor the determinants of these intermediate HIV-1-induced clinical manifestations are fully established. Their significance has nevertheless grown increasingly clear."*
> Kaslow & Francis, 1998, p. 110.

Where no immunological measures are available, the clinical symptoms (particularly in aggregate) are a helpful indicator of disease progression.

In 1990 there was also uncertainly whether children with HIV would show a similar pattern of neurological involvement to infected adults. Early studies in the USA (e.g. Belman *et al,*1985; Epstein *et al,*1985 and 1986) suggested a very high incidence of encephalopathy in HIV infected children. However European studies indicated that fewer than 20% of infants with HIV had neuro-developmental problems (e.g. Blanche *et al,*1990; Tardieu *et al,*1995). It is likely that such differences in the frequency of CNS dysfunction result from other risk factors, such as poor health care, malnutrition or *in utero* exposure to drugs. Recent studies such as Havens *et al* (1994) have confirmed that these factors contribute to the developmental status of infants with HIV infection.

Some infected children showed a rapid decline in several areas of functioning, others had less obvious impairment or had developmental scores within the normal age range (Sirois *et al,*1998). In an attempt to summarise the effects of HIV disease, several different developmental courses of the disease in

children were reported (e.g. progressive encephalopathy including loss of previously acquired milestones by Belman, 1994 and Brouwers *et al* 1991). Structural brain changes such as cerebral atrophy, white matter abnormalities and calcification of the basal ganglia were frequently identified, but the relationship of these physiological changes to functional impairment is poorly understood.

It is likely that those not infected during gestation / peri-natally will display different effects of infection. What little research has explicitly addressed the findings for those children not infected by the vertical route, has shown that for the most part such children perform within age expectations, so long as they remain asymptomatic (e.g. Sirois and Hill, 1993; Whitt *et al,* 1993). However there is a dearth of research on the long term effects of asymptomatic infection in children and on the effects for those who do not yet meet the criteria for an AIDS diagnosis.

1.4.2: Neurological manifestations of opportunistic infections associated with AIDS

Some of the neurological symptoms of HIV infection can be attributed directly to opportunistic infections. In CDC Stage IV opportunistic infections appear to be a direct result of the effect of HIV infection on "cellular immunity" (i.e. lowered levels of CD4 lymphocytes). McArthur (1989) provided a useful overview of the neurological manifestations which may result from opportunistic infections (summarised below).

In the USA and UK the most common infections and their consequences McArthur (1989) included:

- *Cerebral toxoplasmosis* which in 1988 was producing *"necrotic multi-focal abscesses in 3-10% of patients with AIDS."*
- *Cryptococcosis* which is usually associated with meningitis and affected 5 - 10% of AIDS patients.
- The *herpes* group of viruses: *herpes simplex, herpes zoster* and *cytomegalovirus* (CMV) can all affect the eye or brain. 5 - 20% of AIDS patients were recorded with progressive visual impairment resulting from CMV retinitis.
- *Progressive multifocal leukoencephalopathy (PML)* results from an opportunistic viral infection and occurred in 4% of AIDS patients.

1.4.3: Summary of the neurological manifestations directly or indirectly resulting from HIV infection / AIDS

Various studies demonstrated that the final stage of HIV infection (AIDS) was associated with physiological damage to the brain. For example: Jakobsen *et al* (1989) used Computerised Tomography (CT scans) to demonstrate increased ventricular size. This shrinkage was associated with shrinkage of the brain tissue itself, it could be due either to cell death or to reduced cell volume. The increased ventricular size was inversely related to neuropsychological functioning in a sample of 26-55 year old *"unselected AIDS patients"* (n=16). Jakobsen *et al* also noted a positive correlation between ventricular size and reaction time in these patients (i.e. larger

ventricles and therefore reduced brain tissue was associated with slower reaction times).

In 1990 it was less clear whether there could be neurological damage directly or indirectly related to the presence of HIV in the earlier stages of HIV related illness. The researchers were beginning to discover some neurological symptoms occur which appeared to be a direct consequence of the HIV infection itself, rather than resulting indirectly from other infections. The mechanism for the development of such neurological symptoms was often unclear, possibilities included neuronal damage resulting from direct viral action and toxicity effects from viral secretions. Other possibilities included "side effects" resulting from damage to other bodily systems, such as auto-immune disorders.

McArthur (1989) provided a useful summary of the directly and indirectly caused neurological symptoms which is reported throughout the following section.

Epstein *et al* (1986, p.678) commented that:

> *"In adults, a sub-acute subcortical dementia has been described, often associated with gait disturbance [Navia et al,1986]. Less commonly seen are pure spastic paraparesis [Petito et al,1985], acute meningitis [Ho et al,1985], and peripheral neuropathy of axonal or demyelinating types [Lipkin et al,1985]."*

Most of the neurological manifestations of HIV infection [sometimes called HIV encephalopathy] are disease stage specific (McArthur,1989):

Stage I: about 3% of patients developed an acute viral *meningitis* as they become infected with the HIV, but most patients have no symptoms at this point. (McArthur,1989).

At Stage II and Stage III: McArthur (1989, p.45) reported that *"silent, sub-clinical spinal fluid abnormalities"* were found quite frequently – 65% of a group infected less than 2 years, and without any neurological signs, showed immunological abnormalities in the CSF. In 50% of those who had been infected for between 12 - 24 months it was possible to achieve a viral culture direct from the CSF.

McArthur (1989, p.45) concluded:

> *"the nervous system is an early target for HIV infection, but that does not necessarily mean that symptoms related to nervous system invasion occur early."*

HIV infected patients were also at higher risk of developing *peripheral neuropathic disorders,* particularly Guillain Barre Syndrome and the chronic *inflammatory demyelinating neuropathies.* Onset could be quite rapid, and sometimes the disorder would progress to "full blown" Guillain Barre with ascending paralysis. Examination showed clear abnormalities of the peripheral nervous tissue: inflammatory cells destroyed the myelin sheaths of

the neurones, though this was thought (McArthur, 1989) to result from immune regulation disorder rather than direct viral action.

Overall, the World Health Organisation's consultative group on neurological impairment concluded that:

"*At present no evidence exists for an increase of* ***clinically significant*** *neurological or neuropsychological abnormalities in HIV carriers* [sic] *(CDC groups II / III) as compared to appropriate controls".* (WHO, 1988) [page number not reported, cited McArthur, 1989].

However, McArthur (1989) was careful to note that the incidence of neurological disorder in the *comparison* groups in most studies was not zero. McArthur (*et al* at Johns Hopkins, Baltimore) reported preliminary findings over 2 years from a longitudinal study *"showed no evidence of significant neurological decline in asymptomatic HIV infected individuals".*

In Stage IV disease: McArthur noted that the most common neurological manifestation was AIDS dementia (ADC) which was classified as a *sub-cortical dementia* resulting finally in a global dysfunction affecting most cognitive functions, including memory, attention, language and praxis.

McArthur (1989) also reported that imaging studies (MRI and CT) indicated that in the earlier stages of the dementia there was a frontal-temporal atrophy, with some bilateral enlargement of the ventricles. In the later stages there

was further ventricular enlargement, with widespread severe atrophy, which was typically more apparent in the fronto-temporal areas. The white matter appeared *"attenuated and rarefied"*. Such radiological abnormalities were apparent in 70+% of HIV dementia patients.

At the cellular level, McArthur (1989) reported that pathological examination indicated that the majority of the damage is to the myelinated tissue and the subcortical nuclear groups (including the thalamus and sometimes the brain stem), whereas the cortex was typically relatively often spared. Occasionally focal areas of abnormality could be observed, where both infection and inflammatory cells were more apparent. The appearance of multinucleated giant cells within the white matter were considered the "most prominent" indicator of HIV infection in a person with AIDS dementia.

Petito (1988) reported that 75 - 80% of those who died of AIDS had neuropathological changes resulting from a variety of disease processes.

The epidemiology of ADC was not clear, though McArthur (1989) offered a "liberal estimate" that 60% of AIDS patients might develop a dementia at some point in their illness.

One of the most important questions concerns whether the HIV itself is the causative agent for the AIDS Dementia Complex (HIV-related Dementia)?

Perry and Marotta (1987) undertook a review of 56 reports covering some 800 cases. They argued argued that the *"mental disturbances"* observed in people with AIDS were due not only to *"profound psychosocial distress, systemic diseases and neoplasms or opportunistic infections within the CNS"* but also to the *"direct neurotoxicity"* of the HIV. They noted that the HIV can produce an array of dysfunctions which can *"mimic many neuropsychiatric disorders",* but the mechanism for the development of dysfunctions was unknown. (Perry and Marotta, 1987, p.221)

Perry and Marotta (1987) were not surprised that the neurotoxic effects of the HIV were not noticed immediately. The research focus on the immunological effects of HIV and the range of other potential causes for mental dysfunction (particularly in children as the majority of child cases are those from the vertical transmission vector) clouded the picture. However a careful history often indicated that the patient had experienced depressive withdrawal, impulsivity or personality change which preceded (often by many months) the onset of the physical symptoms of immune deficiency. In addition, mental status examination of AIDS patients often revealed disorientation and memory loss which seemed

> *"inordinately severe and disproportionate to the clinical status"*
> (Perry and Marotta, 1987, p.222).

Perry and Marotta (1987) cited an early review of the first 52 AIDS patients admitted to The New York Hospital. Perry and Tross (1984) reported that at least 65% of patients had clear evidence of Organic Mental Syndrome (DSM-

III-R), an incidence described as more than double that for the acute medical wards. They added other "clues" for the neurotoxicity:

- The frequency of peripheral neuropathies
  [Britton and Miller, 1984; Jeantils *et al,*1986]

- Atypical psychoses or major affective disorders in patients with no prior psychiatric history [Perry and Jacobsen, (1986)]

- Abnormal brain images (CT and MRI)
  [Levy *et al.*, 1986, Navia *et al.* 1986b]

- Recovery of HIV from the CSF of patients with AIDS related meningitis or dementia, and in symptomatic patients with neurological symptoms but not yet a diagnosis of AIDS. [Ho *et al.*, 1986]

- Isolation of HIV in brain biopsy specimens
  [Gabuzda *et al,*1986; Gartner *et al,*1986; J. Levy *et al*,1985]

Post-mortem examinations provided further evidence of direct HIV neurotoxicity:

- The virus was detected in the CNS (J. Levy *et al,*1985; Gabuzda *et al,*1986).

- HIV-specific immunoglobulins have been noted in patients with AIDS-related neurological symptoms (Resnick, *et al,*1985).
- Various groups showed that mono-nucleated and multi-nucleated macrophages support replication of HIV in the brain (Koenig *et al,*1986; Shaw *et al,*1985; Wiley *et al,*1986).

Investigators obtained mixed results on the extent of the correlation between HIV dementia and neuropathology. Researchers such as Navia *et al* (1986a) found over 90% of patients with signs of dementia had brains which were histopathologically abnormal. Whereas Johnson and McArthur (1986) found that in one third of those with significant dementia, the histopathology was "bland"; but also that in half of the *non*-dementia cases there were prominent histopathological changes.

Perry and Marotta (1987, p.223) commented that such contradictions should be anticipated because the definitions lacked precision and clinical assessments were not yet standardised. They concluded:

> *"...available studies of patients with AIDS suggest the ultimate risk of dementia after HIV infection is high."* Perry and Marotta (1987, p.223).

However, concerns about different norms for differing risk groups on neuropsychological tests, appropriate control groups should always be recruited.

Perry and Marotta (1987, p.225) summarised the signs and symptoms reported in a range of studies on adults as:

"forgetfulness; loss of concentration; disorientation; delirium; slowness of thought; aphasia; apraxia; deterioration of handwriting; apathy; social withdrawal; dysphoric mood; vegetative depression; delusions; paranoia; regressed behaviour; organic psychosis; somatic complaints; and socio-pathic behaviour."

From studies of perinatally infected children, they add: *"cognitive deficits and psychosocial developmental lags"* [ibid.].

However Perry and Marotta (1987) also discussed the appropriateness of the use of the term "sub-cortical dementia" to describe the neuropathy in AIDS. This term was originally introduced by Albert *et al* (1974) and expanded by McHugh and Folstein (1976) and Cummings and Benson (1984). Perry and Marotta (1987) cite a critical discussion of the term by Whitehouse (1986) which suggests "sub-cortical dementia" can induce a vagueness of terminology which may lead researchers to not offer precise clinical[1] description. This point is important, particularly as some neuroanatomical and neurofluorescent data challenge the notion of a clear demarcation between the cortical and sub-cortical areas. The criticism is particularly relevant to the research into HIV encephalopathy as the neuropathy is known to extend throughout the gray and white matter. Perry and Marotta (1987) noted particularly that HIV patients do show evidence of *cortical* dysfunction – including memory loss; inability to draw a clock; frontal lobe release signs; finger agnosia; dyscalculia and left / right disorientation [(Navia *et al,*1986 a,

b); Nielsen *et al* (1984); Perry and Jacobsen, 1986); Marotta *et al,*("in prep" – 1987)].

Perry and Marotta (1987) offered clinicians seven guidelines for early identification of HIV-induced mental changes based on their review of the literature:

1. Any patient presenting with mental disturbance could have an HIV infection, but the index of suspicion *"will be strongest for those in designated high risk groups"* (Perry and Marotta 1987, p. 228).

2. A careful history which reveals no prior personal or family history of mental disturbance *"yet reveals recent signs of forgetfulness, impulsivity, personality change, apathy, weakness, withdrawal, and impaired judgement"* (*ibid.).*

3. A mental status examination which includes sensori-motor tasks may detect non-verbal deficits.

4. Abnormalities on neurological examination (e.g. peripheral neuropathy, vacuolar neuropathy and diffuse motor findings may initially predominate over cognitive and behaviour symptoms at presentation).

5. CSF, EEG, CT and (especially) MRI may appear abnormal before cognitive decline is apparent.

6. An extensive neuropsychological battery which addresses both cortical and sub-cortical functions may disclose a subtle impairment not apparent from other measures.

7. Longitudinal follow-up over months / years may be necessary to distinguish the organic disorder from "*the psychosocial stress responses and psychological morbidity so prevalent in HIV populations (Perry and Jacobsen, 1986).*" [*ibid.* p. 229]

Perry and Marotta (1987) also reported that the course of HIV dementia had not been well documented. Most patients involved in the various studies were diagnosed only a few weeks before death, but a retrospective evaluation of their histories indicated subtle, prodromal changes. These changes included: forgetfulness, poor concentration, fatigue, and depressive withdrawal; and they often appeared to pre-date the onset of opportunistic infections etc., suggesting a *"prolonged insidious course of HIV-induced dementia"* (Perry and Marotta, 1987, p.229).

Various prospective studies were established in the 1980s and early 1990s in order to discover more about neuropsychological functioning in asymptomatic HIV patients. In the meantime Perry and Marotta recommended treatment aimed at specific symptoms and *"tentatively suggest the following 3 general strategies for the clinician to consider":*

a) psychoeducation to permit patients to make informed choices about their personal and financial arrangements while still competent to do so.

b) Pharmacotherapy for specific symptoms and infections.

c) Psychosocial support e.g. "titration of external stimuli"; correcting misperceptions and distortions; providing orientation, structure and familiar surroundings; monitoring personal and financial affairs; and prevention of destructive impulsive acts (e.g. violence, suicide and HIV transmission).

Belman *et al* (1988, p.34) commented that

> *"Accumulating evidence suggests that AIDS encephalopathy results from HIV infection of the CNS."*

They cited a number of sources of evidence in support of this hypothesis from various studies:

- The demonstration of HIV nucleotide sequences in the brain tissue of children and adults with encephalopathy (Shaw *et al,*1985).
- Localisation of HIV antigen by immuno-histological techniques in brain endothelial cells (Wiley *et al,*1986).
- Macrophages and multi-nucleated cells (Koenig *et al,*1986; Pumarola-Sune *et al,*1987).
- Identification of viral particles with multinucleated cells and macrophages (Koenig *et al,*1986; Sharer *et al,*1985).

Belman *et al* (1988) added that (p.34)

> *"The route and timing of HIV CNS invasion and the pathogenic mechanisms by which this retrovirus causes the encephalopathy are uncertain".*

McArthur (1989) reviewed the evidence that the HIV itself was the aetiological agent in the ADC. He reported that first: dementia was not apparent in other patients with immunosuppression (e.g. bone marrow transplant cases) and was apparently specific to HIV infection. Second: a number of the other retroviruses were known to result in encephalitic damage in their animal hosts. Finally, there was direct (viral culture or other) evidence of HIV infection in the brain or CSF of ADC patients and imaging studies could often distinguish other causative factors.

1.4.4: Summary of the neurological manifestations of HIV / AIDS in children

As there are relatively few references in this area prior to 1990, and as this study is concerned particularly with the effects of HIV on the cognitive functioning of younger people, each study will be briefly summarised here and in Table 1.4.1.3.

Epstein *et al* (1986)

[see also Table 1.4.1A –1. 4.1D]

Epstein *et al* (1986) provided one of the few early reports specifically concerned with HIV effects on children in the USA. Their 36 participants (19 boys, 17 girls) were 26 children with a vertically acquired infection, and 10 children who had acquired HIV from blood products, including two with haemophilia. Their participants' age range was from 2 months to 11 years, with an average age of 13 months at the time of initial diagnosis of HIV

Table 1.4.4A from Epstein *et al* (1986, p.680, Table 1): Clinical staging of HIV infection and neurologic dysfunction*.

Clinical stage	Progressive[1] encephalopathy	Static encephalopathy	"Normal"
AIDS	16	4	0
AIDS-related complex (ARC)	3	3	6
Asymptomatic HIV positive	1	0	2

*results are expressed as numbers of children.

Table 1.4.4B from Epstein *et al* (1986, Table 2): Neurologic findings of progressive encephalopathy

(the table's presentation is modified slightly but there is no change to the content)

Finding	No. of patients affected
Loss of developmental milestones or sub-cortical dementia	19 / 20
Impaired brain growth - Secondary microcephaly - Cortical atrophy on CT scan	19/20 12/20 14/16
Generalised weakness with pyramidal signs	19/20
Pseudobulbar palsy[2]	6/16
Ataxia[3]	4/8
Seizures[4]	5/20
Myoclonus	2/20
Extrapyramidal rigidity	3/20

[1] Essential features for diagnosis of progressive encephalopathy: loss of developmental milestones, intellectual deterioration, or progressive motor deficits.
[2] Not reliably evaluated in infants less than 12 months of age
[3] evaluated only in children who achieved independent ambulation.
[4] Seizures were most usually an isolated event, often in the context of a febrile illness.

Table 1.4.4C from Epstein *et al* (1986, Table 3): developmental assessment in children with HIV
(the table's presentation is modified slightly but there is no change to the content)

Clinical stage	Normal	Abnormal Motor and Perceptual-motor skills	Abnormal expressive and receptive language skills	Abnormal cognitive functioning by age-appropriate psychometric testing
AIDS (n = 9)	0	9	7	5
ARC (n = 5)	3	2	2	0
Asymptomatic HIV positive (n = 1)	0	1	0	0

Table 1.4.4D from Epstein *et al* (1986, Table 7): Neuropathologic Findings in patients (n = 14) with progressive encephalopathy
(the table's presentation is modified slightly but there is no change to the content)

Finding	No.of patients
Gross pathology: diminished brain weight for age	14 / 14
Microscopic pathology: - vascular inflammation	7
- vascular calcification	13
- Inflammatory cell infiltrates	10
- Multi-nucleated cells	10
- White matter change (pallor / astrocytosis)	12
- Other: cytomegalovirus (CMV) inclusions / positive immunoperoxidase	2

Epstein *et al* were able to observe the children for periods ranging from 6 – 50 months, between October 1981 and December 1985, during which time 13 with an AIDS diagnosis died, and two changed diagnosis from ARC to AIDS. Epstein *et al* used a range of methods to assess the children, including formal developmental assessment (where feasible), CT scans and analysis of blood and CSF as well as histopathological study of neural tissue.

Epstein *et al* summarised the neurologic findings [reproduced here as Table 1.4.1B] for the progressive encephalopathy group. They presented their data on developmental milestones [reproduced here as Table 1.4.1C].

Epstein *et al* commented that

> *"Delay of motor milestones was the most prominent feature in the younger children."* ... *"The older children tended to have perceptual motor deficits."* ... *"In general, delays in motor function, perceptual motor function, and expressive speech were more common and of greater severity than delays in receptive speech or purely cognitive deficits. These findings consistently corresponded to the clinical neurodevelopmental assessment in these children."*
>
> Epstein *et al* (1986, p. 681).

The Epstein *et al* (1986) CT scans most commonly showed cerebral atrophy combined with secondary enlargement of the sub-arachnoid spaces and ventricles in 14 of 16 cases of "progressive encephalopathy". Similar, but milder, changes were apparent in 2 of 8 of the "static neuropathy" cases and in 1 of the 6 "neurologically normal" children. In 5 of the progressive cases

there was bilateral, symmetrical calcification[2] of the basal ganglia, 3 of these cases also had calcification of the peri-ventricular white matter.

Epstein *et al*'s CSF findings indicated further abnormalities in 10/26 cases: abnormal findings were present only in those with both AIDS and progressive neuropathy. In all cases cultures for infectious agents[3] in the CSF were negative.

In terms of the clinical outcome in the Epstein *et al* study, the progressive encephalopathy was significantly more likely ($p < 0.001$ on Fisher's Exact test) to be associated with death: 13/20 deaths in the progressive group compared to 0/8 for the static encephalopathy and 0/8 for the "normal" neuropathologic examination. The progressive condition was also associated with a more rapid death: averaging 7.9 months (range 3 – 14 months) from first onset of neurologic signs. The others had survived an average of 8 months (range 2 – 20 months) at the time of reporting. No child identified as having a progressive neurologic deficit showed either improvement or recovery. Two children initially considered to have static conditions "evolved" to a progressive pattern.

In those cases where post-mortem neuropathologic evaluation was possible, a number of findings were reported, summarised below [reproduced here as Table 1.4.1D].

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[2] With one exception there was strikingly symmetrical and in all cases this was confined to the anatomic borders of the basal ganglia, without mass effect or oedema.

The inflammatory cell infiltrates were distributed throughout the grey and white matter, but were most prominent in the deep structures, including the basal ganglia and brain stem. There were also prominent inflammatory changes and calcifications of the small / medium sized blood vessels – most often in the basal ganglia and deep hemispheric white matter. Throughout the white matter a "reactive astrocytosis" was observed, accompanied by myelin pallor in some cases (distinct de-myelination was not observed).

Epstein *et al* (1986) concluded that more than 50% of children with HIV develop a progressive neuropathy, though this does not usually occur until AIDS develops. They proposed that such encephalopathy should be included in the classification of the spectrum of HIV disorders in children and that it is a *"grave prognostic sign"* (p.684) and added:

"Our data strongly suggest that this encephalopathy is the result of HIV infection of the brain and that the outcome is usually fatal." (p.684)

"Brain infection probably occurs early and is persistent. HIV is most likely responsible for the progressive encephalopathy seen in these children." (p.686)

[3] Note that at this time it was not possible to culture HIV from a CSF sample at their Institution.

In terms of the location of the damage to the brain, Epstein *et al* (1986) concluded:

"The major neurologic findings point to a sub-cortical location of the pathologic process." (p.685)

Other symptoms also point to sub-cortical damage, including the pyramidal signs. The impaired brain growth and micropathologic findings all indicated diffuse white matter disease, as did the rarity of seizures and prominence of motor deficits, rather than cognitive deficits.

Belman *et al* (1988)

Like Epstein *et al*, Belman *et al* (1988) also looked specifically at the neurologic syndromes affecting children with HIV infection. Of their 68 patients, 50 had an AIDS diagnosis, and all of the remainder were symptomatic (ARC). The age range was 6 weeks to 13 years (median age 16 months) and the study included two haemophiliacs and five others had had blood products or transfusions (two of whom were also born to mothers in high risk groups), the remaining 61[4] appeared to have been vertical infections. All participants had serum antibodies for HIV.

Belman *et al* (1988) found that 61 of their 68 patients had ***CNS dysfunction*** (48 of 50 AIDS, 13 of 18 ARC). The severity of this dysfunction varied, as did the course of the infection. The most frequent manifestations included:

- acquired microcephaly,

[4] Belman et al cited this figure as 63 cases, but this is because they included the 2 children in the transfusion group who were also at risk of vertical infection.

- cognitive deficits and
- bilateral pyramidal tract signs.
- Lymphomas of the CNS (3 cases),
- cerebrovascular accidents [CVAs] (2 cases) and
- CNS infections by "conventional" pathogens were documented in 8 children (approx. 11%).

Belman *et al* (1988) noted that in only 5 of these cases were the CNS infections opportunistic – a lower rate than one encounters in adult AIDS patients.

The ***disease course*** was variable:

11 children had a sub-acute presentation and steadily progressive disease.

31 had a course which was *"more indolent and began with a plateau"* (Belman *et al,*1988, p.29), of these, 13 exhibited further deterioration but 3 improved.

17 had a static course, with cognitive deficits alone apparent in 7 children; a further 10 had both neurologic impairment and cognitive deficits.

Developmental delays were apparent in most of the Belman *et al* (1988) cases:

24/50 AIDS and 10/18 ARC patients had attained early motor milestones at appropriate ages (i.e. normal development);

9/50 AIDS and 7/18 ARC patients showed mild delays; and

12/50 AIDS and 2/18 ARC patients had moderate to severe developmental delays. (No data were available for a further 4 cases).[5]

The majority of patients had deficits in both fine and gross motor skills and in language skills; they had less extensive deficits in social skills. A follow-up study demonstrated that 58/68 of the children deviated from the normal developmental progression.

Cognitive deficits were identified by Belman *et al* (1988) through formal psychometric evaluation in 38/45 (28 AIDS and 17 ARC) cases:

2 AIDS and 5 ARC achieved scores in the normal range.

12 AIDS and 7 ARC scored in the borderline – mild range.

14 AIDS and 5 ARC had scores indicating moderate to profound mental retardation.

Of the remaining 23 cases, for whom there were no formal psychometric evaluations, serial neurologic assessment categorised 12 as having severe impairment ("dementia").

Motor signs:

42/50 AIDS and 10/18 ARC cases reported by Belman *et al* (1988) had bilateral pyramidal tract signs;

mild-moderate spastic diparesis (32 cases);

spastic paraparesis (4 cases);

spastic quadriparesis (16 cases).

Progressive pyramidal tract (long tract) signs were documented in 21/50 AIDS and 4/18 ARC patients.

3 cases developed a hemiparesis which progressed into bi-lateral involvement in 2 cases.

4 of the children had generalised muscle weakness.

Extra-pyramidal and Cerebellar signs:

Belman *et al* (1988) reported that as their illness advanced, 4 AIDS cases developed rigidity and one had dystonic posturing. 6 children had ataxia and 3 tremor.

Seizures were uncommon, they occurred only in 5 AIDS and 1 ARC patient.

CSF findings were normal in all but 4 patients, all of whom had a sub-acute and progressive course and progressive marked attenuation of the white matter on CT.

Neuroradiological studies reported by Belman *et al* (1988) of those with a "sub-acute progressive" or "plateau" course revealed cerebral atrophy, white matter abnormalities and calcification of the basal ganglia in 23/25 cases. CT studies on those with a static course were normal or showed mild atrophy, poor brain growth was documented by serial head measurements.

[5] Note that these figures (which are exactly as cited by Belman *et al*, 1988) do not in fact add up correctly – there appear to be 5 (AIDS) cases whose data are not cited, rather than 4; and there are a total of 19 (not 18) ARC cases cited.

9/10 children who had both cognitive and neurologic deficits were given CT scans, 6 patients had mild-moderate atrophy, in 3 cases this was associated with mild white matter abnormalities.
Of the 7 children with only cognitive impairments, 2 scans showed atrophy and 4 were "normal" (no scan was available for the 7th case).

Post-mortem findings included varying degrees of inflammatory response, multinucleated cells, calcific vasculopathy and pyramidal tract degeneration. All patients had calcification of the basal ganglia and often the centrum semi-ovale. This varied from scattered small vessel calcospherites to large calcific parenchymal deposits.

There were also certain indications consistent with the disruption of the blood-brain barrier, oedema or inflammation (e.g. calcification of the basal ganglia). It was noted that symptoms could result from persistent HIV CNS dysfunction *causing "cellular dysfunction and metabolic perturbations"* (p. 35).

1.4.5: Psychological / cognitive effects of HIV

In the various studies described in this introduction the researchers have often reported the use of test batteries which address the psychological / cognitive effects of HIV alongside its effects on the various neurophysiological measures. In part this is because it is difficult to disentangle the various signs and symptoms into such artificial categories as psychological, cognitive or neurophysiological effects. Among the symptoms experienced by HIV

positive people are various neuropsychiatric and neuropsychological effects. These symptoms have at least eight possible sources:

i. people with HIV infection frequently experience social isolation and stigma, often resulting from public ignorance, and this experience imposes additional strains which increase their risk of psychological distress.

ii. The person is well aware that their condition is likely to be associated with deteriorating health and eventually death. In common with many other chronic / terminal conditions there is the potential for psychological effects as a result of this stress.

iii. The person is also aware of the potential risk to their sexual partners and their children during pregnancy & birth. Again distress may result from this knowledge, even when reasonable precautions are taken to avoid infection.

iv. Pre-morbid factors such as previous emotional disturbance, prior head injury or alcohol / substance abuse, pre-existing specific learning difficulty or other events (e.g. congenital or perinatal damage, previous infection by other agents, ingestion of toxins, etc.) could also influence post-infection symptomatology.

v. The person may have a history of using pharmacological agents (prescribed or illicit) which may have resulted in damage to the CNS.

vi. Several of the opportunistic infections, particularly the cytomegalovirus, were known to directly or indirectly affect the brain and nervous system and give rise to organic damage which results in neuropsychological or neuropsychiatric symptoms.

vii. Many of the drugs used to treat the symptoms of HIV infection were relatively new, or were being used for much longer periods of time than had previously been necessary, therefore it was possible that some of the symptoms being observed were unwanted effects of the pharmacotherapy.

viii. There is also the probability that the virus itself invades the Central Nervous System (CNS), causing organic damage resulting in a range of symptoms including, ultimately "AIDS-related Dementia Complex" (ADC). The *mechanisms* of such damage were not known in 1990. Researchers were aware of the likelihood that ADC was a result of either direct viral action (neuron death due into HIV invasion of those cells) or indirect effects (e.g. toxins released by the HIV within the CNS, resulting in neuron death).

It can be difficult or impossible to determine the extent to which a symptom results from the understandable psychological distress, or from pre-morbid factors, or from the physiological effects of micro-organisms, or from drug action.

It is necessary to consider separately (as far as this is possible) the effects on psychological status in the asymptomatic and symptomatic phases of infection. Hence the effects in CDC Stage II – III are reported in the appropriate sections and the effects occurring in CDC Stage IV are reported in that section.

1.4.6: Psychiatric effects of HIV

Various studies have demonstrated the range of neuropsychiatric effects of HIV, for example:

Perry and Marotta (1987, p. 225) described HIV as similar to syphilis: a *"great imitator"* capable of simulating almost any psychiatric disorder, even in the early stages of infection.

Riccio *et al* (1988) reported a range of psychiatric disorders in HIV patients including: anxiety, depression, suicidal behaviour, psychosis, delirium and dementia. Riccio added that

> *"the clinical impression is that their prevalence and severity appear to increase with the severity of their physical illness"* [and the early signs of the ADC include] *"apathy, withdrawal, lethargy, mental slowing, reduced concentration and attention, subtle personality changes, problems with retaining new information and motor inco-ordination" ."*
> (Riccio *et al,*1989, p.1)

1.4.7: The post-1990 literature

There is a far more extensive literature dating from after 1990, and therefore the following section will deal only with a selection of those articles.

The literature remains inconclusive on the question of whether there are subtle but measurable cognitive changes in the earlier, asymptomatic, stages of HIV infection.

Taking just one form of psychometric test – the reaction time task - as an example:

> Ayuso-Mateos *et al* (2000, p. 72) commented that *"overt cognitive deficits are not characteristic of asymptomatic HIV infection"* though they speculated that, as survey results have been variable, conventional neuropsychological tests may be insufficiently sensitive to any changes. Ayuso-Mateos *et al* (2000) advocated the use of computerised assessments of reaction time as a more sensitive measure of cognitive functioning.
>
> Ayuso-Mateos *et al* (2000) found that in their own study of N = 65 HIV positives from an IVDU population (other "risk groups" having been addressed elsewhere) there was evidence that such subtle deficits can occur. Although they noted the possibility that drug use itself is a factor, they controlled for this with an HIV negative control group. Their HIV negative group included 14.3% individuals whose performance was classified as "abnormal" (more than 2sd below the

mean) and their HIV positive group, who were all CDC category A or B, had 30.8% cases with abnormal performance - a significant difference on a chi-square test ($p < 0.05$). There was also a significant difference ($p < 0.01$) in the simple reaction times of HIV positive and negative groups, even after controlling for differences in age and educational level.

Ayuso-Mateos *et al* (2000) cited some other studies indicating subtle changes in reaction time in asymptomatic HIV populations:

Ollo *et al* (1991) demonstrated, using auditory and visual stimulation of event-related potentials, that both stimulus evaluation (amplitude) and processing speed (latency) were affected in the earliest stages of HIV infection, even before changes were measurable by standard assessments.

Martin *et al* (1992) and Wilkie *et al* (1990) demonstrated slower processing for *complex* reaction time [CRT] tasks, but not for simple reaction tasks [RT], in the early stages of infection.

Karlsen *et al* (1992) found that seropositives had reduced speed and increased variability of RT (24 HIV positives; 27 HIV negatives) which were more pronounced on simple tasks.

Llorente *et al* (1998) tested the Multicentre AIDS Cohort Study (MACS) cohort on the same computerised RT assessment as did Ayuso-Mateos *et al* (2000) but did not find a significant difference in RT scores between the asymptomatic and HIV negative groups. Ayuso-Mateos *et al* speculate that this could be because there is a major difference in the pre-morbid functioning of the participants. The MACS cohort is relatively better educated than the IVDU group, who may therefore have a "lower cognitive reserve" (Ayuso-Mateos *et al,* 2000, p. 76) and hence be more likely to show the effects of any underlying neuropathological process.

Therefore, even considering just one area of psychometric assessment, reaction time, there is disagreement about whether skills are affected early in HIV, or not. There is recognition that this inconsistency of findings may result from either:

- differences of methodology (e.g. using computerised assessments or more traditional ones)

or

- test sensitivity or from differences in participant groups (e.g. some being better educated and / or having a greater "cognitive reserve")

or

- from other extraneous factors not yet identified.

There have also been some important contributions to the debate concerning whether it is possible and appropriate to identify clusters of participants who have a particular pattern of symptoms and how this clustering should be

achieved. The following studies (in addition to their contribution of descriptions of the effects of HIV) deal with some of those methodological issues.

Van Gorp *et al* (1993) [see also Table 1.4.2A]

Van Gorp *et al* (1993) suggested that the search for a *unitary* pattern of neuropsychological deficits in HIV-related disease may be misguided and therefore the use of overall *group mean* scores for entire HIV Positive groups is inappropriate. Instead they sought "meaningful" sub-groups representing reproducible, identifiable sub-types of HIV-1 related cognitive decline using a multi-variate classification approach.

Van Gorp *et al* used empirical methods to derive three sub-types of neuropsychological performance in a large pooled sample (N = 298) of HIV positive gay or bisexual men from three sites. The sub-types were

- Cluster 1: normal for both mood and neuropsychological assessment;
- Cluster 2: depressed participants with psychomotor slowing and lowered verbal memory; and
- Cluster 3: participants with cognitive and motor impairment and "normal" mood.

The sample included those considered at particular risk of HIV-associated cognitive motor complex, but specifically excluded any participants whose history indicated any other neurological risk factors. This is a slightly unusual inclusion / exclusion strategy, though the exclusion of those with other risk

Table 1.4.7 A: Summary of Van Gorp's (1993) findings:

Total sample N = 298 HIV positive gay or bi-sexual men Sub-types	%age of outlier* neuropsychological test scores is noted for each sub-type	Proportion of Symptomatic & Asymptomatic cases:
"unimpaired" n = 117 (39% of total sample)	13% outliers n = 15	72% Asymptomatic **28% Symptomatic**
"***depressed*** with psycho-motor *slowing* and lowered verbal memory performance" n = 83 (28% of total sample)	61% outliers n = 51	39% Asymptomatic **61% Symptomatic.**
"**normal mood** with *lowered* overall neuro-psychological (cognitive & motor) performance" n = 98 (33% of total sample)	63% outliers n = 62	48% Asymptomatic **52% Symptomatic.**

* outlier scores were defined as those 2 or more standard deviations below the mean score of a demographically comparable group of HIV Negative men on the same neuropsychological tests.

factors certainly helps to sift out the effects of HIV from potential confounding variables.

Sub-types did not differ in terms of their length of education, therefore it is unlikely that sub-type 3 simply had the lowest pre-morbid performance. There was no significant relationship between measures of clinical functioning and sub-type membership - so sub-types did not simply represent those in whom immuno-suppression was most advanced, nor were the sub-types from different locations.

Van Gorp *et al* noted that most research on HIV infection has characterised its effect as a sub-cortical dementia[6]. The most notable deficits appeared on measures of psychomotor speed, complex reaction time, memory and changes in affect.

Van Gorp *et al* used a Principal Components Analysis to produce a five factor solution which accounted for 68% of the overall variance. It was noted that the solution was essentially similar to that reported by Miller *et al* (1990) for the full MACS[7] cohort. The factors identified were (each accounting for between 7-34% of the variance):

1. "Psychomotor Speed" 2. "Mood and Affect"
3. "Visuo-spatial Ability" 4. "Verbal Ability"
5. "Verbal Memory"

[6] originally referred to as the AIDS Dementia Complex; now termed "the HIV-associated cognitive / motor complex" AAN AIDS Task Force, (1991).

[7] MACS stands for Multicentre AIDS Cohort Study (in the USA).

In a Cluster Analysis to determine whether there were identifiable sub-types among the four cohorts of HIV positive men *"a significant association was found between symptom status and cluster grouping"* (page 68). Van Gorp *et al* concluded that they had demonstrated three stable and reproducible sub-types of neuropsychological performance.

Van Gorp *et al* also speculated that their Cluster 3 (normal mood + motor / cognitive impairments) may represent those who *"have sustained non-focal, diffuse CNS changes secondary to HIV infection"* (page 70). The authors added that a subset of these participants may have met the criteria for the HIV-associated cognitive/motor complex.

Van Gorp *et al* also commented that the identification of their Cluster 2 (depressed mood + psychomotor slowing + poor verbal memory) is intriguing, because the pattern is remarkably similar to those described for other sub-cortical dementias - which may support the claim of a sub-cortical pattern of damage in HIV infection.

Van Gorp *et al* (1993) summarised:

> "[their] *results suggest that the* [participants] *across clusters differed in both pattern and level of neuro-psychological test performance"* (page 68).

ANOVA revealed that Cluster 1 ("unimpaired") participants performed significantly better on virtually all neuropsychological variables whereas Clusters 2 and 3 showed significant differences in their performance.

Despite a clear demonstration of different clusters of difficulties in their sample, Van Gorp *et al* did not comment on what might have created the differences between their clusters, except for a general acceptance of the notion that there are differing patterns of neuropsychological decline. For example, they did not discuss the possibilities of differing strains of the virus having differential effects on the nervous system.

Wess *et al* (1998)

[See also Table 1.4.2B]

Wess *et al* (1998) cited several studies which indicated that in some individuals subtle cognitive impairments appeared in sensitive tests of processing speed (e.g. computerised reaction time) *before* immuno-suppression is apparent [Bornstein *et al* (1993); Martin *et al* (1993); Martin *et al* (1992); Miller *et al* (1991); Wilkie *et al* (1990)].

Wess *et al* also cited a number of studies of self-perceptions of HIV seropositive participants' own cognitive status. They noted that the findings were inconclusive: some researchers reported correlations between self-reported neurological / cognitive problems (e.g. Mapou *et al,*(1993) suggested that there may be <u>two</u> groups of HIV positive people who complain of difficulties: those whose complaints reflect an organically based

Table 1.4.7 B Summary of Wess *et al* (1998) results:

Sample	HIV positive group n = 95	HIV negative group
73 male 46 female Total N = 119	n = 56 AIDS n = 14 symptomatic n = 25 asymptomatic The AIDS group rated themselves significantly slower (on the SRSS) than both the HIV Positive asymptomatic group and the HIV Negative group.	The HIV Positives rated their degree of slowness significantly higher ($p \leq 0.01$) than the HIV Negatives. There was no significant difference ($p > 0.05$) between the SRSS ratings of the HIV Positive non-AIDS group and the HIV Negatives.
Findings of no significant correlation ($p > 0.05$) of the SRSS with	- indices of Generalised Anxiety Disorder, Alcohol Dependence or Substance Dependence. - the Trail Making Test part B and word generation (letters). - tests of general verbal skills (WAIS-R Vocabulary and the NART) and of visuo-spatial skills (WMS-R Visual Reproduction Copy).	No significant correlation between SRSS score and other neuropsychological scores.
Findings of significant correlations ($p < 0.05$) of the SRSS with:	- indices of major depressive disorder and dysthymia. **- psychometric tests in which timing was critical**: the WAIS-R Digit Symbol, word generation (animals) and the Trail Making Test Part A. **- tests of memory** Verbal free Recall; WMS-R Visual Reproduction Immediate & Delayed Recall.	

neuropsychological deficit, and those whose complaints reflect an affective disorder. Other researchers found self-reports of cognitive difficulties to be correlated with psychiatric symptomatology rather than neuropsychological measures (e.g. Perkins *et al,*1995).

Wess *et al* argued that the self-rating inventories (SIs) typically used in psychiatry may be insufficient to capture the broader psychomotor phenomena specifically associated with HIV infection, where the fronto-cortical system is the most affected cerebral system [e.g. Everall *et al,*1991]. They developed their own Self Report Slowness Scale (SRSS) to quantify complaints of cognitive and motor slowness with regard to activities of daily living.

Wess *et al* (1998) concluded that their battery showed differential sensitivity which may reflect the specific nature of the cognitive dysfunctions associated with HIV disease. The SRSS scores correlated with those for word generation, non-verbal memory and information processing speed, suggesting that an observed pattern of memory deficit and slowed cognition was associated with self-reported slowness. In addition SRSS ratings correlated with the presence of clinical depression. These observations *"converge with the notion of frontal-sub-cortical system dysfunction in the etiology of neuropsychological deficits (Grant & Martin, 1994) and mood-related disorders (Cummings, 1993) in HIV infection."* (Wess *et al* (1998) pg. 98).

The Wess *et al* (1998) SRSS appears useful in that it allows one to categorise the *severity* of the complaints of slowness (rather than simply the presence or absence of such complaints identified in many other measures) which may be useful in evaluation of interventions. It may therefore be a more appropriate psychometric instrument than many of the classical self-rating questionnaires, in part because it is less likely to include questions concerned with physical fatigue etc. which may be confounded in the case of HIV positive participants.

Grassi *et al* (1999)

Grassi *et al* (1999) assessed a group of HIV positive people who were not drug or alcohol users and who had no cerebral or psychiatric illness and were not acutely ill at the time of assessment. All were in CDC stage A or B and their CD4 counts were used to complete the classification (A1, A2 or A3; B1, B2 or B3). They administered a range of neuropsychological tests plus the Zung Scale for depression.

Grassi *et al*'s results indicated that their groupings did not differ in terms of educational level or age, and there were no differences in neuropsychological performance when participants were grouped according solely to disease stage. However when grouping was according to CD4 count *within* disease stage there were significant differences – in Stage A (n = 242) neuropsychological performance reduced as CD4 count dropped; a trend which was less evident in Stage B, possibly because of a smaller number of participants (n = 86). When the same data were analysed *solely* in terms of CD4 count, it was evident that:

"Overall HIVDA[8] and psychometric battery scores were worse in the CD4 < 200/μl group." Grassi *et al* (1999, p. 227).

They note that this CD4 level (<200/μl) has been considered an important threshold in the natural history of the disease.

NB: they were able to exclude depression as a possible confounding variable as there were no differences in Zung scale score across the groups, even in the advanced disease stages.

Grassi *et al* concluded that

"CD4 count [was] *more closely associated with cognitive performance than disease stage".* Grassi *et al* (1999, p. 228) and therefore this level of CD4 is the best predictor of further decline.

Osowiecki *et al* (2000)

Osowiecki *et al* (2000) argued that, as in other medical conditions, neurocognitive and emotional distress and immune functioning strongly affect the quality of life of HIV positive women (N = 36). This is particularly significant given the prevalence of psychiatric and psychosocial difficulties among people infected with HIV. Affective disturbances are particularly common in HIV positive people (Perkins *et al,*1994) and those people with major depression have been shown to have greater "impairment" in all domains of quality of life than non-depressed HIV positive people (Ling *et al,*1998; Swindells *et al,*1999; Manaldo *et al,*1998). Neurocognitive impairment is also relatively common in HIV related illness (Dunbar and Brew,

[8] HIVDA = the HIV dementia assessment

1996; Heaton *et al,*1995) with impairments of attention, information processing speed, mental flexibility and response fluency being most commonly reported. Such cognitive impairments affect ability to cope with tasks of everyday living, and so may lead to loss of independence, ultimately affecting quality of life. Osowiecki *et al* (2000) demonstrated that in their sample the positive association between neurocognitive function and quality of life was independent of severity of emotional distress (there was also a strong relationship between severity of emotional distress and quality of life).

Suarez *et al* (2001)

Suarez *et al* (2001) reported that the milder forms of cognitive impairments in HIV infection are known as "HIV-1 associated minor cognitive / motor disorders" [DSM IV, 1994] which are characterised by impaired motor speed and working memory, with relative sparing of attention, episodic memory and visuo-constructive abilities.

The severe forms of HIV associated cognitive impairment affect approximately 15% of people with AIDS (McArthur *et al,*1993) and are known as the "HIV-1 associated dementia complex (ADC)" [DSM IV, 1994].

The ADC is

"characterised by psychomotor slowing, memory impairment, disturbances in complex attentional tasks and executive functioning , as well as behavioural manifestations [Bornstein *et al,*1993]*".* (Suarez *et al,*2001, p.195).

Suarez *et al* (2001) reported that the sub-cortical pattern is similar in minor cognitive / motor disorders and ADC. They added:

"The relationships between cognitive dysfunction, HIV-1 load in plasma and the CSF, and neuropathological lesions have been examined in several studies [14-21], but the pathogenesis of ADC and minor cognitive / motor disorders in this setting remains unclear." [p. 196]

[Refs 14-21 cited were: Seilhean *et al* (1993); Glass *et al* (1993); Hestad *et al* (1993); Everall *et al* (1994); Bell *et al* (1996); Di Sclafani *et al* (1997); Stout *et al* (1998); Chang *et al* (1999)].

Suarez *et al* (2001) reported their neuropsychological study of N = 91 participants, some of whom (n = 53) were receiving HAART (Highly Active Antiretroviral Therapy). They confirmed the Sacktor *et al* (1999) and Price *et al* (1999) findings that HAART improves existing cognitive impairments in HIV positive patients. They identified specific improvements in psychomotor speed, verbal anterograde memory, and executive functions. Suarez *et al* also showed that there may be separate pathological mechanisms producing psychomotor and cognitive dysfunction, since these abilities had differing rates of improvement - psychomotor speed showed continuing improvement, whereas the other skills tended to improve initially then plateau.

Stankoff *et al* (2001)

Stankoff *et al* (2001) conducted a small comparative prospective study (N = 22) of the effect of HAART (highly active anti-retroviral therapy) on cognitive dysfunction. All participants had a CD4 count below 200/mm^3, either at study entry or in the preceding year, 11 cases were classified, against DSM-IV

criteria, as cognitively unimpaired; while the remaining 11 cases were 9 people with mild cognitive impairment and 2 people with dementia. 19 participants were on HAART (duration 1-15 months) at study entry and the remaining 2 began within 2 months.

Stankoff *et al* conducted a neuropsychological battery at 3 month intervals for 9 months[9] (Mini Mental State Examination, Mattis Dementia Rating Scale, Trail Making A 7 B, Purdue Pegboard & Grober & Buschke tests plus the Montgomery & Asberg Depression rating Scale). As a small scale study, their results can be considered preliminary at best, but are said to indicate that:

> *"HAART partially reverses both clinical and metabolic abnormalities. Long term follow-up will be needed to determine if patients with cognitive deficits recover."* Stankoff *et al* (2001, p. 115).

1.4.9: Summary of the neurological manifestations of HIV / AIDS in children (post-1990)

As in the literature concerned with adult patients, there has been a substantial increase in the amount of research published concerning children with HIV infection. Therefore a selection of studies are presented here and summarised in Table 1.4.2.3.

There are relatively few studies of this cohort and therefore those which exist are discussed in some depth below.

[9] note that some participants were assessed only once.

Belman (1997)

Belman (1997) reviewed the effects of HIV on the nervous system with particular attention to infants, children and adolescents. She noted that the earliest cases of children with AIDS were formally reported in the literature in 1983 (e.g. Ammann *et al,*1983).

Belman divided the neurological and neurobehavioural disorders into:

a) those symptoms thought to be directly related to HIV-1 including the clinically recognised syndromes with cognitive, motor and behavioural manifestation which are related to CNS HIV-1 infection and HIV-associated CNS disease.
b) Secondary CNS complications, e.g. those associated with immunosuppression or distinct systemic AIDS-related conditions (including infections caused by pathogens other than HIV, neoplasms and CVAs.
c) Metabolic and endocrinological derangements associated with systemic HIV-1 infection and AIDS-related disorders. These may be amenable to therapy and are therefore transient and reversible.
d) Toxic or metabolic complications of drug treatments.

Children born to HIV positive mothers may also be affected by non-HIV related CNS complications resulting from premature delivery, particularly where mothers have "high risk" lifestyles. Belman *et al* (1993) and Nozyce *et al* (1994) conducted prospective longitudinal studies of the neurological status of non-infected infants born to sero-positive mothers (i.e. the study considered: does *in utero* exposure to HIV affect the growing nervous system

where the child is uninfected?). They found that "sero-reverters"[10] aged 3 - 24 months did not differ from matched controls born of HIV negative mothers, though there were some children with neurological and neurodevelopmental disorders in both groups, not surprisingly these were associated with "high risk" maternal behaviours.

Belman (1997) noted that the proliferation of terminology to describe neurological disorders and a frequent lack of accompanying clear descriptors led to ambiguity in the early literature. A consensus report (AANATF, 1991) suggested the term *HIV-associated progressive encephalopathy (PE) of childhood* and enumerated the well described late manifestations of CNS disease. However Belman commented that this paper did not delineate the early manifestations, rate of CNS progression or state of CNS disease. She added that the terms "sub-acute progressive", "plateau" (with improvement / deterioration) and "static / stable" were introduced to represent the differing patterns of symptoms (Belman *et al,*1988).

Belman (1997, p. 230) reported that continued clinical studies suggested that

> *"the spectrum and diversity of "HIV-1 encephalopathy" is much wider than previously appreciated."*

For the remainder of the article she used the term "HIV-1 associated CNS disease syndromes" to refer to

[10] Sero-reverters are infants born with HIV antibodies who cease testing positive for antibodies at some point after birth and who are not infected by the HIV.

"the CNS disorders (including PE) with a constellation of cognitive, motor, and behavioural manifestations currently believed to be related to the CNS effects of HIV-1." (Belman,1997, p. 230).

Belman (1997) described the clinical manifestations of the HIV-1 associated CNS disease syndromes: the most frequently signs are:

- cognitive impairment (evidenced by developmental delays),
- poor brain growth
- abnormalities of tone

Other signs may be:

- motor dysfunction (e.g. rigidity and opisthotonic posturing may be present, often superimposed upon spasticity).
- Cerebellar signs
- Mood and behaviour problems may manifest as the disease progresses.

Belman (1997) and colleagues have proposed a disease classification for children with HIV / AIDS [see Appendix 14 for a summary]. The classification is based upon:

a) age of onset of clinically apparent disease and

b) domains of function most affected and the severity of those deficits

d) rate and pattern of disease progression.

In infants the most severe disorder is *HIV-1 associated progressive encephalopathy* [PE] which typically onsets at 3-8 months but may begin as late as the second year. The characteristics of HIV-1 associated PE are:

i. Progressive cortico-spinal tract signs with

ii. concomitant loss of previously acquired motor milestones or "markedly deviant" rate of motor skill acquisition

iii. acquired microcephaly

iv. marked "delays" in mental development.

The final picture is a withdrawn and apathetic child who has quadriparesis and markedly impaired higher cortical function. The pattern of decline in the PE is variable: some have a rapid deterioration, others an episodic course with episodes of relative stability.

The other pattern reported by Belman (1997) in infants is a less severe and more "indolent" course commencing in the first two years: this is sometimes called the "plateau" course.

In school age children the signs observed included:

- Cognitive decline
- Loss of interest in school work
- Social withdrawal
- Emotional lability
- Decreased attention
- Psychomotor slowing
- Decline in composite IQ score (with advancing disease)
- Motor dysfunction of varying severity (hyper-relfexia, clumsiness, poor fine motor ability and co-ordination)
- Progressive long tract signs

- Cerebellar signs
- Myelopathy

Like the younger children, the end stage of CNS disease is a child with apathy and "abulia" (i.e. feeding / swallowing difficulties). Once again though there is a second sub-group of children at this age who have a more static disease course.

Belman (1997, p. 235) discussed neurobehavioural and cognitive signs in children and noted:

> *"The question of early signs of HIV-1 related neuropsychological impairment and domains affected remains unanswered."*

She went on to report that various studies have indicated effects on various forms of cognitive function in children who were symptomatic but did not have "overt clinical evidence" of PE and who were functioning at the borderline, low or average ranges of cognitive ability (e.g. Brouwers *et al,* 1994). The domains affected included: attention, perceptual motor function, expressive language and memory. Affective disorders were also noted in these patients.

Attention: Belman (1997) noted that for adult patients attentional difficulties are a common early symptom of HIV-1 associated dementia. In addition, the onset of *new* dysfunctions of attention have been described in children who developed PE. *"Therefore, attentional problems may indeed be an early behavioural manifestation of HIV-associated CNS disease."* (p.236). However the clinicians' problem is that ADD and ADHD are relatively common in the

general population – particularly in children with premature births, *in utero* exposure to drugs / alcohol and those with a strong family history of ADHD (Brouwers *et al,*1994). Therefore powerful research designs with rigorous control group comparisons are essential to establish whether the ADD / ADHD rate is significantly higher in the HIV positive population than in the appropriate comparator groups. Two such studies (Aylward *et al,*1992; Havens *et al,*1994) have shown high rates of ADHD in HIV positives, sero-reverters and controls and they suspect background / genetic factors common to these risk groups rather than HIV itself. Belman (1997) recommends that ADHD should not be attributed to HIV-1 CNS disease unless of recent onset.

Visuospatial and organisational skills: Belman 1997) noted that several studies involving a variety of risk groups have demonstrated that there are small but consistent differences in motor speed, visual scanning, and cognitive flexibility.

Language: various investigators have noted language dysfunctions, typically these are more apparent in language production than reception. Infants who develop PE may stop vocalising and older children may regress to use of "telegraphic speech" or single words (Belman, 1997). Even those without overt CNS symptoms have been recorded as having delayed language and impaired expressive functioning (e.g. Condini *et al,*1991). Havens *et al* (1993) studied the language and cognitive functioning of three groups and found that the HIV positives had short term memory deficits on the 1Stanford –Binet (4^{th} edition) test compared to sero-reverters and controls, but that there were no

differences in general intelligence or language function. Wolters *et al* (1995) compared HIV positive children with their non-infected siblings: the HIV positive group formed two sub-groups, those with and those without encephalopathy. Wolters *et al* noted that only the HIV positive sub-groups had expressive language impairment and this was marked in the encephalic group, affecting both receptive and expressive function. There was correlated neuroimaging evidence of cerebral atrophy in the encephalopathic sub-group.

Affective functions: Belman (1997) gives the signs of neurobehavioural dysfunction in children with HIV-1 associated CNS disease, including flattened affect, social unresponsiveness, withdrawal, and declining interest in the environment. Other indications may include: depression, volatile mood, agitation, extreme impulsiveness and altered attentional functioning.

Belman also commented on the epidemiology. She (1997, p. 237) noted that

> *"the true incidence of pediatric HIV-1 associated CNS disease is not yet known."*

The literature is difficult to collate and interpret because of differing terminology, varied study populations and the range of study designs. The prevalence rates for neurological involvement cited by Belman (1997) vary from 20 - 75%, the higher rates tending to occur where children with advanced disease are included. The frequency of occurrence of PE as the first AIDS defining illness has ranged from 12-16%, which is said to be in contrast to adult studies where the rates are 0.8% - 2.2%.

Belman (1997, p. 237) commented that:

"Extrapolating form the experiences of many investigators, it appears that in general HIV-1 associated CNS disease parallels progression and severity of immunodeficiency and systemic disease."

Belman (1997) reported that though **CSF studies** were limited to small numbers of patients, they did indicate early invasion of the CNS by HIV-1. The **neuro-imaging findings**, such as CT scans, typically demonstrate a variable degree of cerebral atrophy and white matter abnormalities. Calcification of the basal ganglia tends to be apparent in younger children and in those with clinical signs of CNS disease than in older children. Less frequently rarefaction of the frontal white matter can be observed. While serial studies often show progressive atrophy and white matter changes or calcification, in some cases there is no apparent change, even where serial head circumference and neurological examination do show progression. Belman (1997) also noted that some children with normal neurological function have mild to moderate atrophy.

Belman (1997) reported that MRI scans also reveal cerebral atrophy, with abnormal signal intensity in the white matter and deep grey structures. Tardieu *et al* (1991) found MRI white matter abnormalities in 40% of child cases, regardless of whether the child had neurological symptoms. Patients with PE were more likely than a "neurologically normal" cohort to show leukomalacia and cerebral atrophy. PET scans have seldom been reported

for child patients, but one study[11] cited by Belman (1997) showed that three children with PE all had diffuse hypometabolism and sub-cortical hypermetabolism, whereas temporo-occipital cortical hypometabolism was seen in the five "neurologically normal" children.

Belman (p. 238) summarised:

> *"Nonetheless there does appear to be a strong correlation between cerebral atrophy and severity of encephalopathy, cognitive dysfunction and aberrant behaviour".*

Belman (1997) reported the n**europhysiological and neuropathological findings** including that EEG studies in children with PE may show diffuse mild to moderate slowing of background rhythm. There may also be abnormal evoked potentials, including increased central latencies and abnormal responses to an increased rate of stimulation.

Belman (1997) also noted that **post-mortem neuropathological examination** of the brains of children with PE provides a range of gross features: variable degrees of cerebral atrophy, ventricular enlargement, widening of sulci, dilation of the ventricles and attentuation of the deep white matter of the cerebrum. Histopathological examination may reveal HIV encephalitis, though this is more common in adults than children. Calcification of the basal ganglia (BG) is the most consistent characteristic, sometimes with mineralisation of the vessels of the centrum semiovale. Such

[11] Belman did not give the reference, though there is mention of Pizzo in the next sentence.

calcification of the BG is not invariably associated with HIV encephalitis: it can occur in the absence of inflammatory disease and where there is no physical sign of acute infection, though accompnying white matter changes and gliosis are common.

HIV leukoencephalopathy is common in paediatric AIDS and is characterised by diffuse staining pallor of the myelin. The damage to the white matter includes myelin loss, reactive astrogliosis and the presence of macrophages and multi-nucleated giant cells, but little or no sign of inflammation.

The most apparent spinal cord changes include myelin pallor restricted to the cortico-spinal tract (CST) which, Belman (1997) noted, is in contrast to adult studies. Some cases have both axonal and myelin pathology, others only myelin changes. Belman (1997, p. 242) commented:

> *"Because the CSTs are the last tracts to myelinate, it is hypothesized that HIV-1 in some way, directly or indirectly, affects the developmental-maturational process. Injury may occur to myelinating glial cells, newly formed myelin, or even antenatally to proliferating glial precursor cells".*

Vascular myelopathy, which is common in adult HIV-1 spinal cord disease, is rare in children, usually occurring only in older children.

Despite the wide acceptance that HIV-1 associated CNS disease (PE) is associated with HIV-1 infection, in neuropathological terms there is, as yet, little evidence of active infection or inflammation and infected cells are seldom

identified. Even once pathological changes are more apparent, there is not a good correlation between the number of infected cells and clinical course. Belman (1997) commented that these findings suggested that factors other than direct neuronal damage by HIV could be important in the pathogenesis, such factors are under active investigation.

The clinical variety of symptoms and signs makes it difficult to predict whether the researchers will eventually find a single pathogenic process which produces a continuum of symptoms over time, or whether multiple processes will be found which will account for differing clinical features. Belman (1997, p. 242) commented that she thought the latter the more likely possibility.

Belman (1997) noted that cerebral atrophy is common in all age groups with HIV infection: studies in adults have identified a specific loss of neurons, with a predominance of loss in the temporal and frontal lobes (e.g. Ketzlen *et al,*1990; Masliah *et al,*1992) and loss of the dendritic arborisations (Price and Perry, 1993). Belman observed that similar studies had not yet been conducted in paediatric AIDS cases.

Belman (1997) also commented on the other forms of nervous system involvement: *peripheral neuropathies* are seldom reported, though Belman speculated whether this is because the children are unable to verbalise those symptoms. Secondary CNS complications are relatively common: e.g. Belman *et al* (1988) found approximately 18% of children in a longitudinal series developed CNS complications. In addition to the usual opportunistic

infections, children are at risk from the common diseases of childhood, the most frequent opportunistic infections are CMV encephalitis, *Candida albicans* meningitis, micro-abscesses and measles encephalitis. CVAs may also complicate the course of HIV-1 disease, resulting from a variety of causes and occurring in virtually any location.

Belman (1997, p. 243-4) is one of very few authors to explicitly discuss the fact that infection may occur in children at a range of ages, and that this could easily affect disease progression. Belman (1997, p. 243-4) commented:

> *"Adult HIV-1 CNS infection and disease occurs in mature, fully developed, and completely myelinated nervous systems. The immune system and CNS elements of the mononuclear phagocyte system (intrinsic microglia) are also fully developed. Vertically transmitted HIV-1 infection occurs in an immature evolving organism. It is believed that HIV invades the CNS early in the course of infection." ...*
> *"The time of fetal infection ([12]i.e. perinatal versus during gestation, and which trimester [early, mid, late?] is likely to be an extremely important factor. The developmental stage of the nervous and immune system when exposed to the direct or indirect effects of the virus must be considered. Innumerable dynamic interactions occur between these two systems during development, which will interact in complex ways with HIV-1 variables. The maturational stage of CNS development*

[12] Open parenthesis without closure is as per the original.

when exposed to the virus will also vary, and this is likely to manifest as different patterns of HIV-1 CNS disease (Belman et al,1990) ". ... "It is possible that the subsequent disease course may be determined in part by tissue distribution, maturity of CD4 cells and bone marrow derived myelomonocytic cells in the immature host (Pizzo et al,1994). Additional factors including differential timing of infection, strain of virus, and increased sequence diversity along with the high mutation rate of specific HIV-1 genes, may allow the virus to evade immune surveillance and persist within the host."

Belman (1997, p. 244) also made an important point about the difficulties of investigation which would apply to any progressive illness in childhood:

"...remember that we are dealing with two different trajectories: (a) the developing brain and (b) a progressive neurological disease. During the designated time period of a particular study or observational period, it is not always clinically apparent (a) if the rate of CNS maturation and development is exceeding the slower rate of the ongoing disease process(es), (b) if the disease process is quiescent, or (c) if the disease process has been abated or arrested by therapeutic interventions."

Wolters *et al* (1999)

Like Belman (1997), Wolters *et al* (1999) reviewed the literature on HIV infection in children, therefore only additional information will be noted here.

Wolters *et al* (1999, p. 105) reported that during "the first decade of pediatric AIDS" (i.e. the 1980s, one assumes) estimates were projecting that 50-90% of children would develop a progressive encephalopathy. More recent studies suggested that approximately 20-50% of children with HIV would exhibit some form of CNS disease (range: mild to severe). Within that group the highest rates of CNS disease would occur in infants (66-75%), and the lowest rate in adolescents (30% according to Englund *et al,*1996). However only approximately 10% of all children with HIV were be expected to display progressive encephalopathy (Lobato *et al,*1995).

Wolters *et al* (1999, p.106) said:

> *"Thus the prevalence of severe neuropsychological deficits in children appears to be declining over time. The more widespread use and earlier initiation of treatment, particularly with combination anti-retroviral therapy, may be preventing, delaying, or reducing the detrimental effects of HIV on the developing brain (McKinney et al,1991; Pizzo and Wilfert, 1994)."*

Like Belman (1997), Wolters *et al* (1999, p. 110) commented on the timing of the infection and its impact on the developing brain:

> *"The timing of productive HIV CNS infection and periods of maximum interference during the development of the immature brain may significantly influence the neuropathogenesis (Civitello et al,1994; DeCarli et al,1993) and impact on the pattern and degree of neurodevelopmental abnormalities (Brouwers et al,1995). For*

example, assuming that structures within the CNS are most vulnerable when they are still being formed, perinatal interference with myelination could affect projection fibres as well as association and commissural connections, resulting in global patterns of deficits with motor abnormalities. Interference in later development would largely affect the commissural connections and the connections with the poles of the cerebral lobes (particularly frontal and temporal) affecting higher cognitive function."

Wolters *et al* (1999) also noted that the use of neuropsychological assessment with composite measures of cognitive function has proven an effective means of assessing the global impact of the disease. However they add that HIV positive children may also exhibit "selective and subtle" impairments which can be missed, or masked, by the global measures (Wolters, Brouwers, Civitello and Moss, 1997)

Wolters *et al* (1999, p.113) reported that:

"Infants are at risk for early neurodevelopmental manifestations associated with HIV that are distinctive from the effects of prematurity and pre-natal drug exposure. Studies have consistently found impaired cognitive as well as motor development [in HIV seropositive infants compared to sero-reverters and controls]*."*

Like Belman (1997), Wolters *et al* (1999) described differing patterns of neurodevelopmental impairment, they add that cognitive delays tend to

develop later and to be less prevalent than motor dysfunctions. However this observation may actually be an artefact of the testing process, since the infant psychometric scales tend to be largely based on motor responses and this is especially true for the youngest age groups.

Wolters *et al* (1999) noted that by 2 years of age approximately 25 - 33% of seropositive infants exhibit moderate to severe cognitive and / or motor dysfunction (i.e. standardised test scores more than 2 standard deviations below the mean). However they also reminded readers that by age 2 years 25 - 33% of seropositive infants were observed to have normal development, the remaining 34 - 50% having mild dysfunction. They added that motor and cognitive deficits were doubly dissociable: either one could occur, or both. Wolters *et al* (1999) also noted that as the most commonly used psychometric tests (the Bayley Scales) measure sensori-motor function then the infant's motor dysfunction could easily confound any assessment of their cognitive skills. Since this is the case, some studies have used the Fagan Test of Infant intelligence [FTII], which assesses visual recognition / memory using an habituation task which does not require a motor response. E.g. Drotar *et al* (1997) found no differences between seropositive infants and controls from Uganda; whereas Swales *et al* (1990) found 33% of HIV positives had dysfunction on the FTII, compared to only 8% of HIV negative controls.

Wolters *et al* (1999, p. 114) reported that

> *"cognitive deficits are less prevalent in school-age and children and adolescents compared to younger children and infants."*

They cited the Englund *et al* (1996) study which indicated that only approx. 9% of older vertically infected children aged 6-18 years had IQ scores more than 2sd below the mean, whereas over 25% of those aged under 6 years had IQ scores below 70. The children in that study had not been exposed to anti-retroviral drugs, so this is not an effect of treatment.

Wolters *et al* (1999, p.115) also briefly reviewed the studies on children with haemophilia [Loveland *et al,*1994; Sirois and Hill, 1993; Whitt *et al,*1993] each of which has been described in some detail elsewhere in this Introduction. They commented (p.115) that these studies did not identify *"overall cognitive deficits attributable to HIV disease at baseline evaluations"*. Wolters *et al* added that longitudinal assessments of haemophiliacs had produced *"mixed results"* with some studies showing subtle decline in HIV positives' performance over time compared to HIV negatives (Sirois and Hill, 1993)

Another study (Smith *et al,*1997) found no such differences.

Wolters *et al* (1999, p.115) were among the very few authors who explicitly commented on the effect of age at infection:

> *"Results from infected children with hemophilia, however, cannot be generalised to children who were vertically infected because hemophiliacs typically acquired HIV later in life, when the brain was more developed."*

Brouwers *et al* did comment on the specific literature relating to correlations between clinical symptoms and brain imaging studies and other disease parameters. Most of this material is similar to that reported by others and so will not be repeated here, but there were some points not already mentioned in this Introduction:

One such point concerns the significantly elevated levels of quinolinic acid (QUIN) in the CSF of children with symptomatic HIV disease (Brouwers, Heyes *et al,*1993; Sei *et al,*1995). QUIN is *"an excitatory neurotoxin produced by stimulated macrophages"* (Wolters *et al,*1999, p.117) the presence of higher than normal levels may be one of the indirect effects of HIV infection of the brain. These elevated QUIN levels were found to be correlated with lower levels of general cognitive functioning. Brouwers, Heyes *et al* reported that after 6 months of anti-retroviral treatment the CSF QUIN levels had fallen and there was a concurrent increase in cognitive function.

Another relevant finding concerns the rate of viral replication in various tissues: Wolters *et al* (1999) noted that the rate of viral replication in the peripheral blood supply may not reflect the rate of replication in the brain or in the lymph nodes and spleen. Sei *et al* (1995) reported that in those with encephalopathy viral levels in the brain tissue tend to be substantially greater, whereas sub-groups of patients tend to have similar viral replication levels in the lymph nodes and spleen. A further study (Sei *et al,*1996) indicated that higher replication rates in the brain were also associated with the presence of abnormal cognitive functioning and that HIV RNA levels in the CSF were

correlated with the extent of cognitive dysfunction. Wolters *et al* (1999, p. 117) commented that:

> *"the activity of the virus within the CNS may be independent of that in the rest of the body, at least in the later stages of the disease".*

Wolters *et al* (1999, p.118-9) also commented on the specific neuropsychological domains affected by HIV disease. They concluded that:

> *"attentional deficits, particularly in sustained attention, may be associated with HIV disease in children, but most likely are only evident in the later stages of the disease or in cases with clear CNS compromise."*

In considering language function, Wolters *et al* (1999) noted that the early studies indicated that expressive function was affected more than receptive language. This was further confirmed, by Wolters, Brouwers *et al* (1995), in symptomatic patients both with and without encephalopathy, even after 24 months of anti-retroviral therapy. Poorer immune status was correlated with poorer language function. Wolters *et al* (1999, p. 119) commented:

> *"the data from these studies suggest that the observed language impairments are associated with the direct effects of HIV on the CNS rather than the effects of environmental factors."*

Studies which considered specific areas of language development showed that school age children had more difficulty with the generation of spontaneous sentences than with repetition of sentences (Wolters, Brouwers *et al,*1995) compared to uninfected peers. This suggested that the underlying

deficit probably related to retrieval of information, semantic knowledge or syntax rather than motor function of working memory. Studies of "expressive emotional language" by Moss *et al,*(1996) and Wolters, Roelofs and Fernandez-Hall, (1995) looked at variables including non-verbal communication (prosody, facial expression, etc.) and expressive symbolic language (verbal language and pantomime). They found that HIV positive children with encephalopathy exhibited less expressive behaviour on most measures than HIV negatives and that this was negatively correlated with CT scan abnormalities. No mention was made of consideration of any alternative explanations: one possibility is that caregivers dealing with HIV positive children limit their own emotional expression because they wish to prevent the child from seeing their distress. Therefore comparisons with other children with life-threatening diseases would be required to determine whether the reported effect is from the action of the HIV.

Certain other cognitive domains have been investigated (e.g. verbal and visuo-spatial memory, visual scanning and visual perception) but there are relatively few studies dealing with each domain, and their methods and findings are inconsistent, so that more research is needed before a summary can be useful.

Wolters *et al* (1999) also discussed the research on the "associated developmental domains" of motor and behavioural functioning, in particular because deficits in such areas can create difficulties for the assessment of cognitive function. The multi-centre study by Englund *et al,*(1996) found that

approx. 23% of paediatric patients without experience of anti-retroviral therapy exhibited some motor dysfunction. The rate differed by age group: those under 1 year had a particularly high rate (45%) and older children and adolescents just 9%.

Wolters *et al* (1999) noted that the specific motor functions affected included gait, strength, co-ordination and muscle tone in infants (Belman, 1994; Englund *et al,*1996). The school-age children had fewer severe motor disturbances, probably due to the lower prevalence of encephalopathy, but could exhibit subtle gross motor dysfunction, particularly affecting the lower extremities (e.g. poorer running agility and speed). Older children and adolescents may also produce subtle perceptual-motor impairments (Epstein *et al,*1986; Parks, 1994) and psychomotor slowing (Belman, 1994; Cohen *et al,*1991). Oral-motor function may be impaired, contributing to reduced expressive language function.

In children with advanced HIV related disease there may be direct behavioural effects including impaired adaptive behaviour (Wolters *et al,*1994); apathy, reduced goal-directed behaviour and flattened affect (Moss *et al,*1994). Wolters *et al* (1999) commented that these symptoms resemble various psychiatric disorders but are now less common because relatively few children get the severe encephalopathy. Additionally indirect behavioural effects such as depression and anxiety may result where children are coping with other psychosocial and medical stressors (Brouwers, Moss *et al,*1994; Moss *et al,*1994). Overall Wolters *et al* noted that behavioural function in HIV

positive children does not differ significantly from HIV negative controls and comparison groups. A greater number of problems occur in those with more adverse life events, which suggests that non-disease related factors may impact psychological functioning.

Wolters *et al* (1999) discussed some of the issues which arise in serial assessment of children with HIV disease:

The assessment battery should be wide ranging with age appropriate measures of general functioning, but because of the possibility that a composite score may mask subtle effects of HIV, comprehensive assessments of specific functions should also be included, particularly for older children. The child's adaptive behaviour should also be assessed, taking into consideration daily functioning and quality of life in the home environment.

The issue of developmental change over time is always prominent in studies of children. Longitudinal assessment is dependent on the use of standardised tests with appropriate and reliable age norms, preferably with small age increments so that comparisons can be made from one assessment to the next. Interpretation of the interval change scores should be undertaken considering the child's abilities in relation to normal developmental growth, the possible effect of HIV disease and of anti-retroviral therapy on the developing brain and the impact of environmental and educational factors on the child's functioning. In longitudinal studies Wolters *et al* recommend continuation

continuation with the form of assessment used at baseline for as long as possible so that "congruent" comparisons may be made over time.

The **frequency of serial assessments and practice effects:** because of differences in likely disease progression shorter intervals are preferable in younger children and longer assessment intervals may be appropriate for older children and adolescents. Practice effects after a one month interval may be as much as 7 points on the WISC III (Wechsler, 1991) but these effects may be smaller with a longer re-test interval; or in children with lower IQ (Tuma and Appelbaum, 1980); or with for those with medical conditions (Farwell *et al* 1990; Moss, Nannis and Poplack, 1981).

Special Test Administration Procedures may be appropriate where the child being assessed is known to already have some specific difficulties (e.g. vision or hearing impairment) making alternative assessments assigned for people with sensory impairments appropriate. Similarly, where the child has symptoms which include fatigue, or short attention span, or inappropriate behaviours then administration must be varied to take these into account for optimal assessment.

Interpretation of neuropsychological test results for planning appropriate interventions must be undertaken within an assessment of the child's full context, drawing upon information from all available sources. E.g. birth information, medical history, developmental and educational history,

environmental and family factors, neurological and neuro-imaging results, behavioural observations and any other examinations.

Brown, Lourie and Pao (2000)

Brown *et al* (2000) noted that by 1998 more than seven million people (worldwide), including one million children, were HIV positive (UNAIDS, 1998). Despite the increasing numbers of people infected, improvements in treatment meant that more than 65% of children survived to at least 5 years of age, and a few, even without treatment, remained asymptomatic for up to 10 years. The authors reviewed 140 studies on HIV and its psychological and social implications. They noted that:

> *"for people living with HIV, medical and social issues are highly inter-related. The social context for many children and adolescents with HIV involves poverty, a lack of resources, and multiple family losses."*
>
> [Brown *et al*,2000, p.81]

Such factors may affect treatment adherence, family relationships, bereavement and illness disclosure while cultural beliefs may influence coping with illness and loss and the nature of community support available.

Brown *et al* (2000) divided their review into four topics:

1. the epidemiology of HIV;
2. neurocognitive development in those infected;
3. the psychological impact of infection;
4. the family and social context of HIV.

These headings were adopted as a means to organise the literature on children with HIV infection and will be re-used here.

Brown *et al* (2000) discussed **the epidemiology of HIV** and recorded that in the USA 25% of new infections involve people under 22 years (and 50% are under 26 years) (Of.N.A.P. 1996). There were more than 2000 children with AIDS under the age of 13 years in the USA, and AIDS was the 6th most frequent cause of death in 15-24 year olds. Infection rates were increasing most rapidly among heterosexual women and young people from ethnic minorities. (NIH, 1997). Demographic data indicated that "families of color" (p. 82) were disproportionately affected: Fahs *et al* (1994) reported 62% of paediatric AIDS patients were African American; 25% Hispanic; 10% white. While there were no natural prevalence data available for children / adolescents. However estimates based on national prevalence data suggested that there were likely to be at least three HIV positive young people for every known AIDS case –
so perhaps 6000 HIV Positive children across the USA, in addition to the 2000 AIDS cases. (Karon *et al,*1996).

Infection routes in the USA are well documented: for adolescents the primary route is by sexual transmission (the most common being homosexual contacts for males and heterosexual contacts for females) (CDC, 1997). A small percentage of cases may have been attributable to sexual abuse (Stolar and Fernandez, 1997). Pediatric AIDS results predominantly from vertical

transmission: 45% have mothers who were IVDUs and a further 20% were born to women whose partner used IV drugs. (Havens *et al,*1994.)

Brown *et al* (2000) also discussed the neurocognitive development in those infected with HIV: many infected children have no medical symptoms and their developmental progress is influenced more by poverty and lack of resources. Where behavioural and developmental symptoms do occur, it is difficult to determine their aetiology. Subtle neuropsychological deficits may result from the CNS effects of HIV infection, but they may also result from pre-natal insults, other diseases (infection, CVA or neoplasm) or environmental factors. Perceived well-being may be directly affected by medical / social factors rather than being directly associated with the virus. Adolescents are more likely to report that their limitations are behavioural and emotional than physical (Remafedi, 1998).

HIV associated progressive encephalopathy is characterised by a triad of symptoms (Mintz *et al,*1996):

A. impaired brain growth

B. progressive motor dysfunction

C. loss / plateauing of developmental milestones.

There is an estimated prevalence in HIV positive children of 13-23% (Lobato *et al,*1995). The course of this disorder may be related to the timing of infection in brain development, the particular strain of HIV, or genetic vulnerabilities. Progressive encephalopathy appears to occur only in the context of general immune suppression. There is no obvious correlation

between encephalopathy and immune status in children (e.g. CD4 count does not correlate with degree of impairment) [Pavlakis *et al* (1994)]. Some sub-groups of younger people (e.g. those with haemophilia) have a lower incidence of HIV-associated neurological disease (Brown *et al,* 2000).

Brown *et al* (2000) noted that various studies document the development of some cognitive and language delays, even in those children who are otherwise asymptomatic, and these signs may be quite subtle. Autopsy findings from progressive encephalopathy cases included:

> *"decreased brain weight, inflammatory changes and calcification of the basal ganglia vessels, white matter degeneration and astrocytosis* (Stolar and Fernandez, 1997)" cited by Brown *et al* (2000).

Some signs were more likely to be apparent, or were only in found in the vertically infected children. Brouwers *et al* 1995 reported that overall CT scan severity rating was "highly predictive" of cognitive functioning. Also that the vertically infected children had a higher rate of CT abnormalities (cortical atrophy, ventricular enlargement and white matter changes) than those infected by transfusion. Intracerebral calcification was seen only in the vertically infected cohort.

Brown *et al* (2000) also mentioned a retrospective study by Papola *et al* (1994) of 90 school age children with HIV indicated that 44% of the 86 HIV positives were functioning in the below average to average intelligence range and 56% had significant language deficits. Bachanus *et al* (1998) reported WISC-III scores and academic achievement ratings of older children with HIV

were significantly below average, with associated impairments of psychological functioning. However, language deficits were associated with poverty in the household and mathematics deficits were associated with the presence of an AIDS diagnosis (direction of causality could not be established in these relationships). The impact of environmental variables is often difficult to distinguish from illness-related factors.

Brown *et al* (2000) noted that some research indicated quite specific deficits: expressive language function was significantly more impaired than receptive function (Wolters *et al,* 1995) in children under 10 years with encephalopathy. Visual-motor skills were also frequently impaired: Frank *et al* (1997) found that status of these skills was the domain most related to disease stage, transmission vector and the children's living environment (n = 27, aged 6-17 years).

Brown *et al* (2000) noted that some early studies indicated that nutritional status could be a mediator of cognitive status, because of the weight loss associated with the later disease stages, however this was not confirmed by later studies. Instead it appears that the correlation between weight gain and decrease in ventricular - brain ratio *could* be linked to malnutrition, but CNS-specific factors and drug treatment factors correlate more closely with cognitive improvement (Brouwers *et al,* 1996).

Brown *et al* (2000) added that anti-retroviral drugs not only halt or inhibit the progression of HIV-disease, but also improve the cognitive functioning of

children with HIV, at least for a limited period of time. This was first reported for ZDV (Zidovudine or AZT) by Pizzo *et al* (1988) and the cognitive improvement was independent of immune status and occurred regardless of whether encephalopathy was present at baseline. There have been subsequent studies which generally support this finding for ZDV and other drugs. The evidence suggests that more effective treatment occurs where there is greater cognitive dysfunction before treatment and where the anti-retroviral agent shows greater CNS penetration (Brouwers *et al,*1994). However other factors which moderate treatment are unclear, especially as the research indicates that any improvements in cognitive functioning are not sustained in many children beyond the first six months of treatment (Tudor-Williams *et al,*1992). This effect emphasises the lack of understanding of the mechanisms of change resulting from anti-retroviral and other treatments, yet standard research methods (e.g. active treatment versus waiting list group comparisons) for looking at these factors cannot be carried out because of the urgency for treatment. Any studies which are conducted are often small scale and may be confounded by variations in patients' prior treatment, varying levels of resistance to certain drugs and variation in disease stage.

Brown *et al* (2000) considered the psychological impact of infection commented that in both adults and children coping with HIV infection is a complex phenomenon involving multiple interacting variables. Increased subjective distress compared to uninfected peers results from both the deterioration of developmental skills and the full range of stressors including disclosure of infection, social ostracism, fears of death and family conflict

(Trad, Kentros, Solomon and Greenblatt, 1994). Plus there are instrumental difficulties in obtaining adequate health care and medication, transport, clothing counselling and recreation (Hansell *et al,*1998). Repeated hospitalisations are known to adversely affect the child's social, language and cognitive development (Task Force on Pediatric AIDS: APA, 1989). Understandably, people of differing cultural backgrounds cope with HIV according to their own social mores and cultural traditions (Williams and Ponton, 1992). Many HIV positive children also have a family history of negative events including death of parent / sibling, forced disclosure of HIV status, or abuse. Brown *et al* also note that psychological dysfunction is also associated with poor social support and school performance, but early intervention may improve the child's quality of life.

Brown *et al* (2000) also summarised the research on psychiatric symptom-atology in HIV infection. Even allowing for the reduced stigmatisation of HIV related illness in the West and improvements in treatments, people with HIV continued to experience considerable distress. In adults with HIV lifetime rates of depressive disorder range from 32-56% (Ferrando, Goldman and Charness, 1997). However there is relatively little research on the psychiatric health of infected children and adolescents and those studies which are published tend to be small scale and report symptoms rather than diagnoses. Several studies suggest that like infected adults, seropositive children experience greater psychological distress than their peers.

Pao *et al* (cited by Brown *et al,* 2000 as "in press") found that of 34 HIV positive adolescents 44% had major depression and 85% had at least one Axis 1 DSM-IV diagnosis on a structured interview measure.

Some parents report increased levels of conduct or hyperactivity problems as well as increased anxiety and depression in their seropositive school-age children (Bose *et al,*1994).

Havens *et al* (1994) found that 26 seropositive children with a history of pre-natal drug-exposure and a mean age just over 7 years scored significantly higher on the sub-scales of the Child Behaviour Checklist dealing with internalising, anxiety / depression, and somatic complaints than did a seronegative matched controls. Controlling for potentially confounding variables (age, race and IQ) did not alter the association between infection and symptomatology.

Bussing and Burket (1993) compared two haemophiliac (6 HIV Positives and 17 HIV Negatives) and one asthmatic (n = 37) groups and found that anxiety was more common in the HIV positives than in either control group. However both haemophiliac groups also had lower levels of intra-familial distress than the asthmatic group, possibly as a result of the support network provided by the US National Hemophilia Programme.

However neurophysiological effects can also be mis-diagnosed as psychiatric disorders: Stuber (1992) reported a case of a child withdrawing because of

physical pain who was given a diagnosis of depression. Since almost 60% of children with HIV experience pain (Yaster and Schechter, 1996), this may affect the quality of their life and increase the risk of psychologisation of physical distress.

At least one study shows the children self-reporting positively: Bose *et al* (1994) reported that children with HIV scored significantly higher on the Perceived Competence Scale for Children which taps global self-concept, and lower on anxiety / depression measures, than did seronegative peers. However the same children's parents did not agree: they rated the HIV positive children significantly more anxious, less socially active & less academically successful than their peers. This parent-child reporting disparity may result from the fact that the sample were asymptomatic, enabling the children to deny their status. Or the parents may have been reflecting their own anxiety in their reports on the children.

Psychiatric treatment of adults with HIV has shown that situation-appropriate anxiety is best treated with cognitive behavioural therapy, while anxiety and other symptoms resulting from HIV encephalopathy may be best addressed with benzodiazepines (Fernandez and Levy, 1994).

Brown *et al* (2000) reported that there was little research on psychiatric treatment of HIV infected children, though it was assumed that similar treatments to those used in non-infected patients would be effective. However

they noted that HIV seropositive patients tend to be more sensitive to the unwanted effects of psychotropic medication than are others.

Brown *et al* (2000) noted that coping responses to HIV infection have been studied extensively, though the research usually involves adults. Grassi *et al* (1998) found 43% of their sample (108 adults) reported poor coping and maladjustment to HIV infection, based on four sub-scales adjusted for HIV from the Mental Adjustment to Cancer (MAC) Scale. Patients reported *"lower fighting spirit, higher hopelessness, anxious pre-occupation and fatalistic attitude."* (Brown *et al* (2000, p. 87). Their poor coping was associated with *"psychological stress, repression of anger, external locus of control and low social support"* (*ibid,* p.87). Grassi *et al* (1998) and other studies supported the view that coping with HIV infection is a complex activity influenced by personality factors, social support and stress. Several adult studies indicated that coping style is a factor in the development of psychiatric / emotional disturbances secondary to infection (Fleishman and Fogel, 1994; Pakenham, Dadds and Terry, 1994). Coping is strongly influenced by cultural attitudes to illness and death (Magana and Magana, 1992).

Brown *et al* (2000) commented that young people living with HIV must cope with multiple conflicts:

- dysphoria from the physiological effects of infection;
- plus emotional distress resulting from a variety of factors including social stigma;
- isolation and hopelessness;

- social withdrawal, depression, anger, confusion and guilt;
- forced disclosure of HIV status;
- anxiety about their prognosis, loss and bereavement and changes in physical appearance (due to wasting and dermatological conditions) (Lewis *et al,*1994).

Children in particular may come to believe that they must have done something dreadful to deserve their condition, and therefore may develop severe guilt reactions (Stuber, 1992). In addition to this non-infected siblings and schoolmates may develop fear of contagion or resentment towards the ill child (Fanos and Wiener, 1994).

According to Brown *et al* all of these stresses result in a range of coping responses: Hardy *et al* (1994) reported that the mothers of HIV positive children described more wishful thinking than did mothers of either cancer patients or healthy children. High self-criticism was also more frequently reported than for mothers of children with cancer, and biological mothers expressed significantly more self-criticism than foster mothers. Overall parental adaptation to the child's illness may be important: Lavigne and Routman (1993) found that parent and family risk factors were more strongly correlated with child adjustment than were specific disease and disability factors.

Brown *et al* (2000) also discussed the family and social context of HIV cited Sherwen and Boland (1994) who demonstrated that the adjustment of young people living with HIV is

"strongly related to contextual parent and family factors and often less related to disease and disability factors" (p.88).

Those family factors include: poverty, parental history of drug use, multiple bereavements, mental health of parents, and ethnic / cultural beliefs.

Brown *et al* (2000) discussed the difficult issue of disclosure to the child and other family members, noting that there are no easy ways to decide when and to whom HIV infection should be disclosed. There are the inevitable anxieties about causing the child distress, having to answer difficult questions on "taboo" subjects such as parental drug use and sexual behaviours, and worries about disclosure to others outside the family. There may be cultural differences: Cohen (1994) showed that most African-American families have disclosed their child's serostatus to immediate family members, whereas only a minority of UK families disclose to their close relatives. The literature around chronic illnesses in general suggests that the child's adjustment is usually better if there is disclosure of developmentally appropriate facts. E.g. Lipson (1994). Brown and DeMaio (1992) reported a case of two haemophiliac adolescents with HIV to illustrate how secrets concerning infection can affect optimal health care and the patient's subsequent psychological adjustment.

1.4.10: Frontal lobe / sub-cortical effects in HIV infection

Bisiacchi *et al* (2000) from Padova, Italy assessed the effect of HIV infection on the neurological functioning of two groups of children born to mothers with

HIV infection (N = 29 HIV positives, 13 seroreverters[13]). The HIV positives were: 5 at CDC stage A; 15 stage B; 9 stage C. All were following an ordinary programme of schooling and none presented learning difficulties. All were neurologically asymptomatic and brain imaging results were also normal.

Bisiacchi *et al*'s test battery addressed a range of cognitive functions including memory, visual-prassic abilities (Street test, spontaneous and copy drawing), language and executive functioning. Their results indicated an abnormal profile *only* for the HIV positive children. In particular all of the infected children (including those in CDC stages A and B) performed worse than the seroreverters on tests of executive functioning. The children in stage C also had significantly poorer performance than controls in the memory and visual-prassic tasks.

Bisiacchi *et al* (2000) argued that such evidence of selective impairment of cognitive functions in neurologically normal children was important because the neuropsychological data may serve as an early marker for CNS malfunction. Since the control group (of similar "disrupted" social background and at risk of vertical transmission) were not affected, one can be more confident that the effects seen are a result of the HIV infection.

Bisiacchi *et al* note that executive dysfunction has now been identified in a range of childhood disorders with varying aetiologies including Turner's

[13] Sero-reverters were those who initially tested positive for the antibody, but "lost" antibodies to HIV in the 15th month of life.

syndrome, phenylketonuria, autism, ADHD (they cited Temple, 1997; Pennington and Ozonoff, 1996).

Bisiacchi *et al* concluded that the selective impairment of executive functions in the early stages of infection was followed in the later stages of illness by memory and visual-prassic dysfunction – hence the memory deficits are *subsequent* to attentional deficits and not simply the result of memory impairments in themselves. This supported their hypothesis that for vertically infected children there is a selective impairment (particularly of executive functioning) in the early stages of illness which may act as a marker for HIV neurological involvement.

Longitudinal studies (Bisiacchi *et al* currently underway in Padova, Italy) will demonstrate whether these subtle signs of neurological dysfunction early in illness are linked to encephalopathy in the longer term.

1.4.11: Psychiatric effects of HIV

Law *et al* (1993) suggested that self-reported depression symptoms (Beck Depression Inventory, [BDI, 1961]) in HIV infected people may *not* be entirely reactive. Depression may reflect, at least partially, the involvement of the CNS. Law *et al* produced significant correlations ($p \leq 0.05$), which were not due to selective endorsement of the somatic items, between both Choice and Simple Reaction Times and Depression scores in their HIV Positive group, but not in an adjustment disorders Control group.

Law *et al* (1990) concluded: *"subtle cognitive changes and depressive symptomatology"* (pg. 184) may be detected at the pre-AIDS stages. They argued, from this study and their previous research on procedural learning and initiation problems (Martin *et al,*1992,1993), that both the mood disturbance and the psychomotor slowing may indicate sub-cortical and frontal (specifically fronto-striatal) effects of HIV infection.

1.4.12: The findings of other studies of people with haemophilia and HIV infection [taken in order of publication].

Kokkevi *et al* (1991) noted that the haemophiliac cohort represent an advantageous group in which to study HIV infection because:

- the epidemiologic cohorts existed prior to infection, so there are well-defined selection procedures.
- They may also be more representative than other "risk groups" and offer greater potential for generalisability of findings to the heterosexual population.
- A haemophiliac HIV negative control group has the potential to be more valid, since heat treatment of blood products has largely removed the fear of infection.

Kokkevi *et al* (1991) reported data from a sample of n = 93 haemophiliacs recruited in Athens, Greece and drawn from a population of 340 haemophiliacs followed regularly at their Haemophilia Centre since 1975. 50.3% of this population tested HIV positive between 1980 and 1985. The HIV positive [n = 60] participants were all *"free of AIDS and ARC"* (*Kokkevi et al,*1991, p.1224) though some were symptomatic and some were undergoing

Zidovudine treatment. There were 29 HIV negative participants. Three further HIV positive and 2 HIV negative cases were excluded because of known neurological disorder, psychosis or illiteracy.

Kokkevi *et al* (1991) conducted a blind screening for psychopathology plus a clinical neurological examination and assessment of mood state and cognitive functioning. Their test battery included:

A brief version of the Wechsler Adult Intelligence Scale (WAIS) consisting of the Vocabulary and Block Design sub-tests.
The Profile of Mood States (POMS) adjective checklist
Beck Depression Scale
The Schuhfried *et al* Vienna Test System (computerised battery described in detail in the report) was administered, including a long term memory test; monotonous attention test, choice reaction test and tracking test.

Note: Kokkevi *et al* (1991, p.1224) claim to have "converted" the WAIS sub-test scores into verbal, performance and full scale IQ scores, but this seems unlikely since the full scale scores cannot be calculated from only two sub-tests. It is possible that they have estimated the IQs from the two sub-test scores, but this method was not justified by the authors and seems unlikely to be valid.

Kokkevi *et al* (1991) compared three groups: those at CDC stages II and III ("asymptomatic"); those at CDC stage IV ("symptomatic") and the HIV

negative controls. These symptomatic and asymptomatic designations do not follow convention, since those in CDC stage III do have some symptoms, though they may not yet meet the criteria for an ARC diagnosis. More recent studies have tended to group participants on the basis of their CD4 count rather than which of the CDC classification criteria they meet.

Kokkevi *et al* (1991) calculated standardised (Z) scores for each variable and also identified potentially confounding variables, which were then used in a regression analysis as covariates.

Kokkevi *et al* (1991) found no differences between their study groups on neurological examination, though a greater proportion of the HIV group had impaired mobility this was attributed to peripheral bleeds or to arthropathies which are common in patients with coagulation disorders. One cannot determine whether the HIV positive sample had more severe haemophilia, which might contribute to this difference, because Kokkevi *et al* (1991) have only reported comparisons with the non-participant group and not differences between the HIV positive and HIV negative participants.

Kokkevi *et al* (1991) also report that the general screening for psychopathology indicated that there was a trend (which did not reach the conventional level of statistical significance, since $p < 0.10$) for a higher proportion of the "symptomatic" (CDC IV) HIV cases to present past or current mood or anxiety disorder. They also confirmed that mood state was not significantly related to cognitive performance in this sample.

Kokkevi *et al* (1991) reported potential confounding variables by reviewing the correlations between various psychometric variables and a number of potential confounds: age, education, haemophilia type and severity of haemophilia were selected. None of these variables were associated with mood state and the correlations with the neuropsychological variables were generally those one would expect: WAIS scores correlated with education (and severity of haemophilia) and other neuropsychological variables were related to education and to age in predictable ways.

The Kokkevi *et al* (1991) data comparing the three study groups is difficult to interpret and to compare with other studies. This is because, instead of presenting the mean scores for each group, as per convention, the authors have instead presented the mean and standard deviation scores for the control (HIV Negative) group and *"the change from a baseline performance of HIV negative subjects, as given by the regression co-efficient (b) for the corresponding indicator variable"* (Kokkevi *et al,*1991, p.1227).
In addition to this, their explanation of the results in the text is also unconventional, since it appears to discuss trends from one study group to another, rather than differences between the performances of groups:

> *"In the cognitive tests battery a statistically significant trend towards lower performance from HIV negative to HIV positive asymptomatic and from HIV positive asymptomatic to HIV positive symptomatic haemophiliacs was observed in the number of correct answers in the monotonous attention test, the global attentional performance, and the*

deviation score of the tracking test [14](*P* = 0.018, 0,049, 0.044 *and* 0.030 *respectively).*" (Kokkevi *et al,*1991, p.1226).

Kokkevi *et al* (1991) summarise by indicating that the HIV positive group's performance was significantly poorer on some tests, including the choice reaction test, global attentional performance and the tracking test deviation score (all $p < 0.05$). The performance of the HIV positive asymptomatic group was consistently slightly poorer than that of the HIV negative controls, but this did not reach statistical significance on any of the variables assessed. They added that, in addition to the symptomatic group's impaired performance, they had evidence of a consistent trend towards poorer performance in the asymptomatic group and that this, combined with data suggesting that some cognitive variables are influenced by *duration of infection,* may be an indication that

"*the mild cognitive impairment observed during the natural history of the HIV infection is a progressive phenomenon not necessarily associated with the clinical expression of HIV infection.*" (Kokkevi *et al,*1991, p. 1228)

This latter statement is somewhat ambiguous. It is not clear whether they mean that the cognitive impairment is the result of the action of HIV, but may be independent of other clinical symptoms, or whether they are suggesting that haemophiliacs may be subject to some other form of progressive cognitive deficit (e.g. perhaps due to the cumulative effects of minor brain bleeds which have neither been identified nor treated).

[14] The unconventional use of upper case P for the probability value is as per the Kokkevi *et al* (1991) text.

The Kokkevi *et al* (1991) study attracted a comment from Selnes and McArthur (1992) in a letter to the journal *AIDS.* Selnes and MacArthur noted that Kokkevi *et al* had not adequately ruled out other possible causes for the differences they identified in cognitive performance. For example there was a trend towards a difference in the participants' mean length of education, and previous studies indicate that education tends to be the major influence on test performance. Selnes and McArthur also note that the effect reported by Kokkevi *et al* appears to be global – affecting all areas of cognitive function, whereas HIV is known to produce specific, not global, deficits in the psychomotor, memory and constructional areas.

Logan *et al* (1993)

Logan *et al* (1993) noted that some early studies had described high levels of emotional disturbance in boys with haemophilia (Browne, Mally and Lane, 1960; Mattson and Gross, 1966). However when those studies were follow-up with appropriately controlled studies of personality traits, mother-child interaction etc. there was no significant difference between the haemophiliac cases and healthy controls (Steinhausen, 1976). Logan *et al* (1993, p. 262) commented that

> *"Differences in methodology, clinic population and support offered, may have contributed to these divergent findings. In general, review articles and descriptive studies without control groups have continued to emphasise the vulnerability of haemophiliac children to psycho-social disorders (Madden et al,1982; Mattson, 1984)".*

Another possible explanation for the claim that haemophiliacs are vulnerable to emotional disturbance is a mistaken assumption by those conducting the reviews and studies without a control group that the rate of such disturbance in a control group would be very close to zero. This assumption has also been a feature of the studies of adults with HIV infection and emphasises the importance of conducting studies with appropriate controls.

Logan *et al* (1993) reported the findings of a research study in Glasgow which aimed to assess the psycho-social impact of haemophilia for affected children living in the West of Scotland. Logan *et al* (1990) had reported the earlier finding that parents' and teachers' ratings and a self-report depression questionnaire indicated that these children were no more behaviourally or emotionally disordered than "diabetic" or "healthy" controls. However there was concern that this methodology might have missed some more subtle disturbances. The 1993 report examined the findings from a semi-structured interview asking the children about their perceptions of their social and school functioning plus their concerns about illness and expectations for the future. Once again Logan *et al* compared the same group of "haemophiliacs" with age and social background matched "diabetic" and "healthy" children.

The target population was 39 families registered with the West Scotland Children's Haemophilia Centre which included one or more children (aged 6 – 15 years) with a bleeding disorder. Where more than one child was affected the elder child was recruited to the study. Thirty two families were recruited to the study. The hospital's diabetic clinic identified suitable age / social class

matched controls and the healthy controls were recruited through GP practices across the region.

The Logan *et al* (1993) sample included 29/32 children whose parents agreed to their recruitment for interview; five of these children were HIV positive and two were aware of their seropositive status. The "haemophiliac" sample included 14 with haemophilia A; 4 with haemophilia B; 6 with von Willebrand's disease; and 5 children with more rare bleeding disorders. Seven of the haemophiliac group were female[15].

Consent for interview was also obtained from 30/32 diabetic children and 32/32 controls. All interviews were conducted by one researcher (Logan), who was unaware of the results of the standardised assessments. The questions concerning future illness were deliberately non-specific (e.g. *"do you ever worry about becoming ill in future?"*).

There was close matching of the groups for gender, age and social class. The data on paternal employment and family structure (e.g. birth order and number of siblings) also showed no significant differences between the groups.

One problem with the Logan *et al* (1993) study is the heterogeneity of their "haemophiliac" group. Although it is understandable, given the rarity of haemophilic disorders, the placement of all those with bleeding disorders in a

[15] Although females with haemophilia A/B are very rare, other bleeding disorders do not have the same gender bias.

single group is not particularly helpful as the disorders have differing treatment patterns and may therefore have differing consequences for different children. A more homogenous group would permit stronger conclusions from the data. Logan *et al* justified the grouping because all of those who attended the Haemophilia Centre were exposed to the same potential stigmatisation resulting from negative media coverage.

Logan *et al* (1993) found that there were no differences in "school function" responses across the groups, except that the "healthy" group were more likely to report that they had been "absent less" than others. The evaluation of leisure activities and social functions indicated that the haemophiliac children were more likely to report a sedentary activity as their preferred after school activity, though this difference did not reach the criterion for statistical significance ($p > 0.05$) and was not associated with increased "solitariness". Most children in all groups played with friends or siblings after school, the haemophiliac children were less likely to report that they played alone. The majority of children in all three groups reported that making friends and obtaining a boy/girlfriend was easy. The majority of children in all groups anticipated marriage and parenthood later on.

Logan *et al* (1993) also asked the children about illness issues: Most of the children considered themselves "as healthy as anyone else" and did not feel more vulnerable to illness than others. A significant proportion ($p < 0.01$) of the haemophiliacs said they were not "able to run and play as much as anyone else". Logan *et al* (1993, p.267) commented that

"the haemophiliac children appeared to acknowledge the reality of some physical limitation but nonetheless regarded themselves as essentially healthy".

Logan *et al* (1993) also asked their participants about concerns regarding transmitting illness to others: they anticipated that this question might enable participants to mention worries about genetic transmission of haemophilia to their offspring, and also might permit mention of HIV infection. In fact worries were more likely ($p < 0.005$) to be expressed by the "healthy" children, who were concerned about passing on everyday infections (coughs or flu) which might then make friends socially unavailable. Two of the haemophilic children did mention genetic transmission of haemophilia.

Questions about possible concerns regarding future illness identified few differences, the haemophiliacs were no more concerned than the other groups. Three HIV negative haemophiliacs did mention concern about AIDS, though in one teenager's case the concern was related to sexual transmission rather than by blood products. One HIV positive and one "healthy" child also *"alluded to concern about AIDS"* (Logan *et al* ,1993, p.267). An open question about "any other worries" drew out concerns about a parent for three children (one haemophiliac and two "healthy" participants).

A set of questions about future employment indicated that the majority of participants in all groups believed that they would be able to get enjoyable work. Those with unemployed fathers were not more pessimistic than others about their own employment prospects. The range of aspirations was similar

across all groups, though Logan *et al* (1993) describe two haemophiliacs' aspirations as "inappropriate" (police and armed forces).

The five HIV positive children (only two were aware of their serostatus) were all currently well. They differed from the HIV negatives on only one question: all doubted they would have children of their own. All five currently felt as healthy as anyone else and four were not concerned about illness transmission. One HIV positive boy who was aware of his serostatus was pessimistic overall: he did not anticipate employment, marriage or parenthood; he was worried about future illness and illness transmission; and thought it would be harder for him to find a girlfriend.

Logan *et al* (1993, p. 270) commented that

> *"The findings were strikingly different from the research teams expectations. It had been anticipated that a high level of distress would be found among the children attending the Haemophilia Clinic and that there would be marked anxiety about AIDS."*

They added:

> *"The questions did identify children who were finding school difficult and who thought making friends was harder for them and some to whom the future looked bleak. However, such children were in the minority and spread across the three groups".*

Logan *et al* (1993) also commented that HIV / AIDS was a major pre-occupation of parents and staff at the time of the research and they were

surprised to find that the children did not appear concerned. The interview questions deliberately did not specifically mention HIV / AIDS, though there were open questions about illness and infection which should have permitted expression of any concerns the children may have had. Logan *et al* acknowledge that the decision not to specifically mention HIV / AIDS could have resulted in a *"failure to identify the full extent of the children's concerns"* (p. 271) but equally one can argue that specific questions might have biased the participants' responses and also provoked anxiety.

1.4.3.3 Sirois and Hill (1993)

Sirois and Hill (1993) conducted a two year longitudinal study of 11 haemophiliacs[16] aged 6 – 16 years recruited through the Louisiana Comprehensive Haemophilia Care Center at Tulane University Medical Center in New Orleans, USA. Five of their participants were HIV negative and six were HIV positive. Their mean duration of infection was 51.5 months (4 years, 3.5 months) at the commencement of the study and 76.8 months (6 years, 4.8 months) at its end. Three HIV positive participants had been aged about four years when infected and the other three had been aged about nine years. All of the HIV positives were asymptomatic when the study began, but one participant received an AIDS diagnosis before the end of the study. None of the participants had Wechsler FSIQ below 80 at baseline.

[16] Sirois and Hill originally recruited 17 participants (80% of those originally contacted through the Hemophilia Center) and six participants withdrew after the baseline assessments – all of whom were HIV+ve, but they did not differ from the remaining HIV+ves on age, duration of HIV infection or WISC-R FSIQ.

The neuropsychological test battery employed by Sirois and Hill (1993) included:

- Bender Visual Motor Gestalt Test (Koppitz, 1975, scoring: McIntosh, Belter, Saylor, Finch and Edwards, 1988)
- Human Figure Drawing (Koppitz, 1968 scoring)
- WISC-R or WAIS-R (Wechsler 1974, 1981) alternated with an abbrevaited version of the Stanford-Binet Intelligence Scale (Thorndike, Hagen and Sattler, 1986a)
- Finger Tapping Test (Knights and Moule, 1967)
- Word Fluency [Form: FAS] (Gaddes and Crockett, 1975)
- Trail Making Test Parts A and B (Reitan, 1986)
- Quick Neurological Screening Test [QNST] (Mutti, Sterling and Spalding, 1978)
- Wide Range Achievement Test- Revised [WRAT-R] (Jastak and Wilkinson, 1984)
- Parental reports from the Child Behaviour Checklist (Achenbach and Edelbrock, 1983) and a Social History Questionnaire developed by Sirois and Hill (1993).

Sirois and Hill (1993) repeated their battery with each participant every 6 months for two years (five assessments). They provided parents with a comprehensive assessment report on each occasion and made recommendations for enhancement of the children's optimal development.

Despite very small samples, Sirois and Hill reported their results as comparisons between (a) HIV positive (n = 6) and HIV negative (n = 5) groups and (b) for age at infection for the HIV positive group (3 younger and 3 older cases). They converted scores to standardised z scores whenever feasible and used the non-parametric Mann-Whitney U test, as is appropriate for small samples.

Sirois and Hill (1993) found that at baseline both HIV+ve and HIV–ve groups scored above the mean on the Wechlser FSIQ, with the HIV+ves producing the higher scores. In terms of the test standardised scores, there were no statistically significant differences in mean scores at any of the points of assessment. However test-retest ("difference") scores comparing the participant's own performance at baseline with their performance at either Time 3 or Time 5 did show some effects. The HIV negatives showed the gradual performance improvements one would expect from repeated assessment. The HIV Positives showed similar improvements at Time 3, but by Time 5 (two years elapsed) there were statistically significant decreases in HIV Positives' scores compared to the HIV Negatives (p values ≤ 0.026 for Verbal, Performance and FSIQs).

The Sirois and Hill (1993) comparison of the children infected at different ages was severely limited because the sample sizes were only n=3 per group. However, they reported that the children infected at a younger age produced significantly poorer standardised scores ($p \leq 0.05$) (which are corrected for age differences) than those who were older at infection, at each of the points

of assessment on the Performance IQ sub-scale. They also had poorer performance on the Wechsler FSIQ and the Verbal IQ sub-scale, but these differences did not reach the criterion for statistical significance ($p > 0.05$). Analysis of this group's difference scores indicated that they showed less improvement on the Performance sub-scale tasks throughout the study than the older children.

Analysis of the results from the other tests in the battery indicated that overall there were no statistically significant differences between the HIV Positive and HIV Negative groups on the Stanford-Binet, the Bender-Gestalt and Finger tapping Tests (p values > 0.05).

The earlier-infected HIV+ves showed poorer performance ($p < 0.05$) on the Stanford Binet Abstract – Reasoning area and on the Bender Gestalt after one year of the study (Time 3), despite having shown an initial greater improvement than the other sub-group on this test. Similarly, the earlier-infected sub-group were initially faster on the Finger Tapping test, an advantage they retained through Time 4, but in the final assessment they scored less well than the older-infected sub-group. However the earlier-infected sub-group did not have globally poorer performance: on the Stanford-Binet Verbal Reasoning tasks they showed improving performance over time, unlike the older-infected sub-group, whose performance in this area declined over time ($p < 0.05$).

Although there were no statistically significant differences between the HIV+ves and HIV-ves on the QNST, the earlier-infected sub-group more frequently displayed neurological difficulties than the older-infected sub-group (chi-squared test, $p < 0.05$).

The results from the WRAT-R results were in contrast to those of the other tests: both the HIV+ve and HIV-ve groups' scores were below average for their ages on all three sub-tests (Reading, Spelling and Arithmetic). This suggests these boys were not achieving up to their potential in basic skills. Sirois and Hill did not discuss the possible reasons, but since both groups are affected, this is likely to be associated with their haemophilia, rather than the HIV, and may be a reflection of the missed schooling which usually results from "bleeds". The groups' performances were similar across all points of assessment, except that the HIV positives' scores at baseline for Reading were higher than the HIV Negatives' scores, but this difference was not statistically significant ($p > 0.05$).

A review of the groups' test-retest (difference) Reading scores suggested that the HIV positives produced less improvement compared to baseline at Times 3, 4 and 5 compared to the HIV Negatives (p values = 0.016; 0.008; 0.056 respectively). The other WRAT-R sub-tests produced no statistically significant differences between the HIV +ve and HIV–ve groups.

The results from parents' responses on the Child Behaviour Checklist indicated very few behaviour problems: only 3/11 participants produced significant issues at any point in the two years of their study.

Overall Sirois and Hill (1993, p. 192) found all of their haemophiliac participants *"remarkably healthy"* with performance within the normal ability and neurological development range, even though the HIV positives had been infected for 5 - 7 years by the end of the study. However they also noted a subtle difference in the patterns of test-retest performance: the HIV negative participants demonstrated the gradually improving performance one would expect, most likely due to the practice effects. The HIV positive participants' performance showed a decline in verbal and perceptual skills. The HIV positive children infected at a younger age had greater difficulty with tasks measuring perceptual motor development and exhibited neurological impairment more frequently than those infected at an older age.

Sirois and Hill (1993, p.192) concluded:

> *"...the HIV+ children failed to show benefit from repeated experience, although at baseline they demonstrated equivalent potential with the HIV- children, suggesting that the HIV+ children were beginning to exhibit generalized difficulties with new learning before symptoms of AIDS appeared."*

Since the children did not appear to have significant behavioural or emotional difficulties and their performance in motor speed and co-ordination (typically

affected by depression) were unimpaired, Sirois and Hill concluded that depression probably did not contribute to the observed group differences.

It is difficult to generalise findings from such a limited size sample, but Sirois and Hill (1993) argued that the findings from their own study and other longitudinal studies of infants diagnosed with ARC / AIDS fit the "percolation theory" model (Nadel, 1990) where CNS damage is not apparent in neuropsychological function until a critical threshold of damage is reached.

Sirois and Hill (1993) also reviewed the literature and suggested that generally in children with AIDS it was common to find regression of certain skills which had previously been acquired. Also in children with AIDS:

- neonatal reflexes persisted beyond 4 months;
- an ataxic gait was common in those old enough to walk;
- brain growth (serial head circumference) was frequently impaired;
- in younger children delays in achievement of motor milestones were apparent;
- regression / severe delays in language development (especially expressive language) are apparent in younger children;
- perceptual-motor dysfunctions were more apparent in older children.
- overall measures of developmental status typically fell within the borderline average to moderately deficient range (Brouwers *et al,* 1991; Epstein *et al* (1986); Ultmann *et al* (1985,1987).

Children with the ARC demonstrated delays in the same ability areas, but their pattern of deficits was far more variable than among those with AIDS (Ultmann *et al* 1985, 1987). The developmental delays were typically less severe, with overall developmental assessment producing results in the average to borderline average range.

Asymptomatic HIV positive children are typically comparable with non-infected children on neurological and psychometric assessment. (Cohen *et al,*1991; Condini *et al,*1991; Loveland and Stebhens, 1991; Neplaz *et al,*1991).

Sirois and Hill (1993, p.179) noted that:

> *"...it has been firmly established that cognitive changes in otherwise asymptomatic HIV-infected individuals are associated with direct infection of the brain by HIV (Falloon, Eddy, Wiener and Pizzo, 1989; Price et al , 1988; Rubinow et al,1988)".*

They added that it was thought the primary site of infection was likely to be the brain in infants / children, and that CNS infection probably occurs early in the course of paediatric HIV disease. The mechanism by which HIV produced the CNS changes was unknown, though there was some early evidence indicating a role for infected macrophages and microglial cells releasing neurotoxins (Giulian *et al,*1990).

Helmstaedter *et al* (1992)

NB: original article is in German, only the Abstract is in English.

Helmstaedter *et al* (1992) reported the follow up, after an 18 month interval, of 62 haemophiliacs from a series of 188 HIV positives who had first been evaluated in 1988. They intended to confirm the cross-sectional results previously obtained and to undertake a longitudinal comparison of the neurocognitive effects of HIV infection in this sample.

At the original assessment (their Table 1) n = 41 participants were in CDC II; n = 18 participants were in CDC III and n = 3 participants were in CDC IV. By the second assessment (their Table 2) there were indications of disease progression: n = 27 in CDC II; n = 19 in CDC III and n = 16 in CDC IV. Overall: 65% of cases did not change disease stage. 27% changed by one stage and 8% had rapid progression from stage II to IV.

The re-assessment by Helmstaedter *et al* (1992) included parallel measures of attention, verbal / non-verbal memory and depression. The findings confirmed the earlier assessment, participants typically had deficits in attention, verbal learning and memory. The deficits were unrelated to T4 / T8 ratio (CD4 : CD8). However only those with a rapid progression pattern had a statistically significant deterioration over time: the remaining participants had inconsistent cognitive performance which was not related to changes in the CD4 : CD8 ratio.

Whitt *et al* (1993)

Whitt *et al* (1993) had access to 125 pediatric patients registered with the University of North Carolina Comprehensive Hemophilia Center who both had

documented Factor VIII or IX deficiency and were aged 4-19 years at the start of the study. On checking it was found that some 21 patients had been lost to follow up (2 deaths, others had moved away) leaving 104 cases. Some 73 people agreed to participate in the study, 71.4% of the HIV positives and 76.8% of the HIV negatives from the original 104 cases. A further ten cases were excluded either because they failed to complete the initial assessment (one HIV+ boy died) or because they changed their minds about participating.

Baseline assessments were completed for 25 HIV positive and 38 HIV negative children. Each of the HIV Positives was matched (for age, race and haemophilia severity) to one of the HIV Negative controls and the remaining controls were kept as a non-matched control group, though five were excluded from the study as they were significantly younger than any of the HIV positives. Therefore the final groups were: 25 matched HIV positive and HIV negative cases plus a further 8 HIV negative controls.

Table 1.4.3.5A: The characteristics of the Whitt *et al* (1993) samples:

Whitt *et al* (1993) Characteristic	**HIV Pos (n = 25)**	**HIV Neg (n = 25)**	**All HIV Neg (n = 33)**
Age at baseline assessment:	13.8 years	13.7 years	13.1 years
Socio-economic status (year of maternal education)	12.0	13.3	13.5
Race – White - Black - Indian/oriental	15 7 3	17 8 0	24 9 0
Severity of haemophilia Severe (< 1%) Moderate (1-5%) Mild (>5%)	25 (100%)	12 (48%) 3 (12%) 10 (40%)	14 (42%) 4 (12%) 15 (46%)
CD4 counts (per mm^3) <200 200-500 >500	407.9 (281.8) 7 (28%) 10 (40%) 8 (32%)	858.5 (246.2) 0 1 (7%) 13 (93%)	883.9 (249.0) 0 1 (6%) 16 (94%)

One of the HIV positive participants was receiving anti-retroviral therapy and two met the CDC criteria for AIDS.

The neuropsychological test battery included assessments selected specifically to consider motor, sensory-perceptual, attention, language, memory, and problem-solving domains hypothesised to show the CNS effects of HIV infection.

The Whitt *et al* (1993) battery consisted of:

- The Wechsler Intelligence Scales (problem solving / memory / sensory-perceptual/ attention / language);
- finger tapping and grooved pegboard and the developmental test of visual-motor integration (motor)
- Finger Localisation; Judgement of Line Orientation; GFW Auditory Discrimination Test (sensory-perceptual)
- Gordon Diagnostic System Vigilance Test, GFW Auditory Selective attention test; Trail Making A and B (Attention)
- Sentence Repetition Test from the Detroit Test of Learning Aptitude; FAS Word Fluency (language)
- Benton Visual retention test (memory)

Whitt *et al* (1993) undertook a process of "data reduction" for two purposes:

1. to determine whether the specified measures were sufficiently inter-related to be summed within each hypothesized domain and
2. to reduce the probability of a Type 1 error.

They then conducted a Principal Components Analysis (PCA) followed by a *Varimax* rotation applied to the *a priori*[17] hypothesized domains. Domain scores were computed as the mean of tests with loading ≥ 0.40 in these analyses. Each domain appears to summarise the information in the selected instruments well, with the proportions of variance accounted for ranging from 53% - 80%. Domain scores were computed as the average z score from the specific tests incorporated into each domain. Tests with negative loadings were negatively weighted (-1 x the test score) when the domain scores were computed.

Whitt *et al* (1993) planned two groups of analyses, the first was a cross-sectional comparison between the HIV positive and HIV negative groups seeking evidence that the HIV positives were performing less well. These analyses took the form of three sets of group comparisons. First the group mean domain scores were subjected to Analyses of Covariance (ANCoVA) using *maternal education* and *haemophilia severity* as potentially confounding covariates (since the HIV positives had mothers who averaged slightly lower levels of education and were likely to have more severe haemophilia). Where significant inter-group differences were detected, subsequent comparisons of the individual variables comprising that domain score were undertaken. The used three separate strategies to test the hypotheses:

- comparison of group means;
- evaluation of pathognomonic signs (cases with scores more than 2sd below the group mean, relative to age norms age);

[17] In this instance the term *a priori* appears to be used to mean that these domains were

- and intra-individual scatter of abilities (indicated by the proportion of Z scores more than 1 sd below the person's own full scale IQ score, a measure of whether the individual participant is achieving their own full potential).

Whitt *et al's* (1993) second group of analyses performed a "within group" evaluation of the data from the HIV positive sample: it examined *"the relationship between neuropsychologic functioning and HIV related illness, especially immune system compromise".* (p.55). For this analysis each participant was allocated to a category based on his CD4 count: <200; 200-500; and >500 cells / mm^3. The CDC classification of symptomatic or asymptomatic disease was evaluated independently.

Whitt *et al* (1993) found that **physiological and neurological examination** did not distinguish between the groups: only two of the HIV participants had significant abnormalities attributable to HIV infection.

The **comparison of group mean domain scores** by ANCoVA demonstrated that the HIV positives' performance was not significantly different from that of the HIV negatives in any of the six neuropsychologic domains. However it is impossible to compare these scores to those achieved by participants in other studies as they are presented in the form of z scores (transformed such that the mean = 0, sd = 1) rather than in the age scaled form.

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logically deduced rather than empirically derived.

Whitt *et al* (1993) recognised that analysis of the summary domain scores might have *"masked relevant HIV group differences"* (p.56) i.e. reduced the sensitivity of the measure to the subtle cognitive changes being sought. Therefore they also undertook descriptive post-hoc analyses comparing HIV positives to HIV negatives, again using *maternal education* and *haemophilia severity* as co-variates. This detailed analysis produced 4 marginally significant results from 22 tests, but all were in the opposite direction to that predicted, such that the HIV positives actually performed marginally better than the HIV negatives on those four variables[18]. This effect disappeared once the severity of haemophilia was removed from the analysis (this co-variate tended to make the analysis more conservative, since all of the HIV positives had severe haemophilia).

The **evaluation of pathognomonic signs** (i.e. scores > 2 sd below group mean on age scaled scores) was intended by Whitt *et al* (1993) to identify any cases of individuals whose performance was significantly poorer than others, but who were too few to have a cumulative effect on the group mean scores. Whitt *et al* (1993) selected 12% frequency as the arbitrary standard for such "deficit" scores in each group relative to age-norm expectations. This strategy identified higher frequencies of "deficient" scores than predicted in the HIV positive group, but the same variables produced equally frequent deficits in the HIV negative group. The areas which produced these high frequencies of deficit scores were:

- Attention Domain sub-test

[18] Whitt *et al* (1993) did not identify the precise variables concerned.

- Motor Domain measures: VMI, Trails B
- Attention domain: Gordon Diagnostic systems total correct and total commissions, GFW Selective Attention
- Visual Processing domain: Judgement of Line Orientation
- Language domain: GFW Auditory Discrimination

The **evaluation of intra-individual scatter of abilities** assessed each participant's performance relative to his potential (as estimated from his Wechsler Full Scale IQ) to identify areas of relatively poor functioning. Whitt *et al* (1993) found that once again there were certain variables for which a proportion of HIV positive participants scored below expectations, but once again a similar frequency of under-achievement occurred in the HIV negative control group. The domains in which this occurred were motor, attention and visual processing.

Tables 1.4.3.5B Whitt *et al* (1993, derived from Table III, p.56) frequencies of deficient scores

Domain	**Sub-test**	**%age with pathognomonic signs**		**%age with intra-individual scatter**	
		HIV+ (n = 25)	HIV- (n = 33)	HIV+ (n = 25)	HIV- (n = 33)
Motor	Motor 1	0	9	8	27
	Motor 2	8	9	20	42
Attention		13	0	25	24
Visual Processing		4	3	8	21
Memory	Memory 1	0	0	16	9
	Memory 2	0	0	17	7
Language		0	0	0	9
Cognition		0	3	0	0

The **intra-group analysis of the HIV positives'** neuropsychological functioning relative to their CDC disease classification produced no significant differences as a function of disease stage. However, it is worth noting that only 2/25 cases were symptomatic and so it may be too early in the disease course for this effect to be apparent. Similarly, the comparison of CD4 count groupings produced no significant relationship between immune function and neuropsychological functioning. Recognising once again that the summative domain scores could be masking the effect being sought, Whitt *et al* (1993) also undertook an evaluation of the 22 individual variables and found that one instrument, the VMI, showed the predicted relationship. The HIV positives with CD4 counts below 200 cells / mm^3 had VMI scores significantly lower ($p < 0.031$) than those with CD4 counts above 200 or above 500 cells / mm^3.

Whitt *et al* (1993, p.58) concluded:

> *"The pattern of neuropsychologic functioning related to age norms in the current cohort of HIV+ children with hemophilia suggested an overall trend toward lower motor, attentional, memory and sensory-perceptual functioning, which parallels earlier reports. However, when the results were contrasted to those in a control group of children who also have hemophilia, no significant differences were apparent. Given the similarities between HIV+ and HIV- groups, it is premature to attribute the age norm-based patterns of subtle neuropsychologic deficit in the infected group profiles to the CNS effects of the HIV."*

Having proceeded to mention the statistical power of their study, and acknowledge the possibilities of type II errors, Whitt *et al* (1993, p. 58) added:

> *"Moreover, it is not the failure to attain a significant statistical difference, but the absence of any data suggesting poorer performance by HIV+ children with hemophilia, that most characterises the current findings."*

Whitt *et al* (1993) also acknowledged the possibility that their study was conducted "too early" in the disease course to detect the subtle changes anticipated. The data were collected an average of 55 months (4 years, 7 months) after 1st January 1985, the date which is thought to approximate the end of the period of peak risk of exposure in the US blood supply. The 1993 report is the baseline for a longitudinal study, which may allow elucidation of some of these factors.

Smith *et al* (1997)

Smith *et al* (1997) undertook a three year longitudinal study of three groups of young people: 13 HIV positive haemophiliacs, 14 HIV negative haemophiliacs and 9 sibling controls[19]. This HIV positive group represented approximately 52% of the infected children known to the Toronto Hemophilia Centre.

At the time of first assessment the Toronto HIV positive group were aged between 6 – 18 years (mean of 12.3 years). The HIV negative haemophiliacs were 6-15 years (mean 9.9 years). The HIV negative sibling controls were 6-15 years (mean 11.8 years). Therefore there were age differences, but these

[19] These figures are after exclusion of 3 cases (all HIV positives) for pre-existing neurological conditions and include only those controls who completed all 3 annual assessments.

were not statistically significant ($p < 0.13$). All haemophiliacs were male. Two siblings were male, the remainder female. The groups did not differ significantly in terms of ethnicity, marital status of parents or socio-economic status.

At study baseline the Toronto HIV positives had been infected for 6 to 7 years. During the study their CD4 counts declined significantly ($p < 0.03$) particularly in years 2-3. (Year 1 mean = 478.2; Year 2 mean = 380.6; and Year 3 mean = 380.0) The neurological status of the HIV positive participants was "normal" throughout the study.

Smith *et al* (1997) reported that anti-retroviral medication was not likely to be a confounding variable. None of the participants in any of the groups was prescribed psychoactive medication during the study.

Smith *et al* (1997) used a very extensive test battery which required 4-6 hours (breaks were permitted!). They reported that there were no statistically significant differences between their groups on the Wechsler Verbal or Performance IQ at any point in the study. Analysis of the Wechsler sub-tests produced only one group effect: the HIV positive performed poorly on the Arithmetic test, particularly in Years 1 and 2. An analysis of variance (ANOVA) showed that both the Block Design and Mazes subtests produced a significant ($p < 0.037$ and $p < 0.017$) Group x Year interaction, though the Mazes assessment is difficult to interpret as only those younger participants completing the WISC-R undertake this task.

Smith *et al's* (1997) assessment of academic achievement using the WRAT-R showed no differences between the groups, but all of the scores were at the lower end of the average range, a contrast to the high-average IQ scores and an indicator that all three groups were under-achieving their potential.

Of the other tests in the Smith *et al* (1997) battery:

- the Story Recall (Delayed) produced a significant ($p < 0.013$) Group x Delay interaction, which was due to relatively poor performance by the HIV Negative group.
- The Rey-Osterrieth Complex Figure Task produced a significant ($p < 0.009$) Group x Condition interaction resulting from improvements in the performance of both haemophiliac groups (HIV Positive and HIV Negative) while the sibling controls had inconsistent results.
- Trail Making Test B produced a Group x Year interaction ($p < 0.003$) reflecting improved performance again for the two haemophilic groups and poorer performance for the sibling controls.
- The Rey Auditory-Verbal Learning List produced one significant Group x Trial interaction ($p < 0.031$) resulting from the HIV positive group having improved performance compared to the other groups on the later trials.
- All other assessments produced no significant differences in performance between the groups.

These results indicated that overall there was no link between HIV infection and cognitive development and were similar to other comparative studies (e.g.

Hilgartner *et al,*1993; Loveland *et al,*1994; Whitt *et al,*1993) which reported no overall impairment in the performance of haemophilic young people. Smith *et al* (1997) highlighted the inconsistency of scores by the control groups, which may reflect the consequences of having a sibling with chronic illness.

Smith *et al* (1997) also mention the possibility that their results represent a Type 2 error because a very large number of statistical tests were undertaken and only eight achieved the conventional 5% probability criterion.

Turning to the results from individual sub-tests Smith *et al* (1997) comment that the difference in performance on the Wechsler Arithmetic scale did not appear to reflect a specific problem with arithmetic (as there were no deficits on the WRAT-R Arithmetic). However they accept that it is possible that the difficulty on this test represents a deficit in attention or working memory or slowed information processing (though there is no evidence of these difficulties from the rest of the test battery).

The US Hemophilia Growth and Development Study

Described in various reports by:

Loveland *et al* (1994); Stehbens *et al* (1997);

Sirois *et al* (1998); Bordeaux et al (2003).

HGDS design

The HGDS was planned as a longitudinal study which was planned to address the underlying processes of HIV infection in a cohort infected at different stages of neurodevelopment. It was deliberately designed as a

"non-therapeutic" (observational) study of the natural history of haemophilia / HIV infection, to be conducted at 14 sites (US Hemophilia Treatment Centers, HTCs). It was designed to avoid as many of the methodological pitfalls of chronic illness research as possible. The study was conducted by multi-disciplinary teams and intended to evaluate both disease progression and *"the dynamic relationships between immune functioning and neurobehavioural functioning."* (Stehbens *et al,* 1997, p.119).

The HGDS included some impressive controls including:

- recruitment of participants across the full range of US Hemophilia Centre locations;
- checks across centres for distribution of exclusions;
- cross-centre training of assessors;
- analysis of the neuroradiological and neuropsychological data (for both validity and clinical opinion) by at least two independent experts in each of those fields.
- All experts were blind to the participants' HIV status.

HGDS Test Battery

Their extensive assessment battery included assessments of:

- physical growth and development;
- immunological status;
- changes in the CNS (neurological exam, MRI scan, EEG);
- neuropsychological investigations which included the Wechsler Intelligence Scales, and various assessments of language, visuo-spatial

skills, memory, attention, fine motor skill, "adaptive behaviour" and "behavioural / emotional" functioning (from parental report).

The neuropsychological test battery selected for the HGDS:

- permitted measurement in nine areas of functioning
- assessments were developmentally appropriate and
- permitted maximum continuity for constructs measured at differing ages.

The annual HGDS battery (function areas in parentheses) included:

- The Wechsler intelligence scales
  (general intelligence / memory / new learning / visuo-spatial perception / language / fine motor control / attention / concentration)
- Rey (1964) Auditory Verbal Learning test (memory / new learning)
- *Color Span (memory / new learning)
- *Benton Visual Retention Test (visuo-spatial perception)
- Judgement of Line Orientation (Benton *et al,*1983) (visuo-spatial perception)
- Wide Range Achievement Test (revised) (academic achievement)
- *Kaufman Assessment Battery for Children (academic achievement)
- Paediatric Behaviour Scale (Lindgren and Koeppl, 1987) (Behavioural / emotional)
- *Child Behaviour Checklist (Behavioural / emotional)
- Word Fluency (FAS) (language)
- Boston Naming Test (language)
- Beery Developmental Test of Visual-motor integration (Beery, 1989) (fine motor control)
- Grooved pegboard (Knights and Norwood, 1979) (fine motor control)
- *Trails A (fine motor control)
- *Trails B (attention / concentration)
- *Token Test, Part V (receptive language)

- *Hiskey-Nebraska Block Design (visuo-spatial reasoning)
- *Sentence Repetition (language reception and expression)

* these tests are used only for those participants whose initial assessment data suggested some abnormality ("trigger" cases).

A shorter battery was applied at the six month intervals, between annual batteries, in order to avoid practice effects.

At baseline all participants and their parents also completed a detailed developmental and educational history and initial medical studies of immune, growth / endocrine and neurological function (including neuroradiological assessment).

The functional areas were chosen in order to determine which areas might be susceptible to the effects of HIV-1 infection or haemophilia as a chronic illness. They are similar to those recommended by Butters *et al* (1990) for adults in a report from the working group for the US National Institute for Mental Health, and also to those recommended by Brouwers *et al* (1990, US National Cancer Institute) for perinatally infected children. Both the NIMH and the NCI batteries were intended to be *"sensitive to cognitive changes thought to occur early in the disease process."* (Stehbens *et al,*1997, p. 121).

The HGDS battery was also intended to address the potential problems of validity and interpretability of neuropsychological follow-up studies as highlighted by Watkins, Brouwers and Huntzinger (1991). To be included, a

psychometric test was required to have available normative data on children, objective scoring and be generally familiar to child psychologists as well as addressing one or more of the nine functional areas of interest.

Unlike most other studies Stehbens *et al* (1997) note that the HGDS introduced the concept of having additional evaluations which are "triggered" if there is anything suggestive of abnormality in the patient's data.

The triggering criteria were:

- Either lower neuropsychological performance at baseline evaluation (-1sd or more below mean in three of the nine function areas)
- Or problems with linear growth
- Or problems with immune function
- Or a decline (from baseline) in neuropsychological performance of similar magnitude to the first criterion in three or more areas on subsequent annual comprehensive examination.

Once "triggered" the participant continued on the more intensive evaluation programme throughout the study.

Loveland *et al* (1994) reported that "Triggering" into the more intensive follow-up protocol proved to be more common than expected for <u>both</u> HIV positive and HIV negative groups: 57/205 (27.8%) and 25/124 (20.2%) of cases respectively. Once adjusted for co-variates this difference was non-significant ($p \leq 0.29$), as was the correlation between CD4 count and "triggering".

Other factors were related to "triggering": having been involved in remedial education ($p < 0.002$) and repeating a grade (year) in school ($p < 0.0001$) were each significantly related. The Revised Index of Occupational Status (SEI measuring socio-economic status) and parental education were each approaching significance at $p < 0.03$ and $p < 0.02$ respectively.

HGDS Participants

The HGDS used stringent inclusion and exclusion criteria.

Those eligible for the study were:

(a) aged between 6 – 18 years on 1st September 1988;

(b) had been seen for comprehensive haemophilia evaluation at the HTC at some point in the two years preceding enrolment; and

(c) had received a minimum of 100 units of factor replacement therapy per kg of body weight each year for the preceding two years (or 9 or more infusions in the same period).

The exclusions affected those without fluent English (as this invalidates the standard neuropsychological tests) and those with pre-existing conditions affecting either cognitive function (IQ lower than 70); or sensory impairment or severe motor impairments (e.g. tremor) likely to affect the neuropsychological tests; or uncontrolled seizures.

The HTCs originally identified a total of 481 potentially eligible participants during a census in Autumn 1988. A total of 333 participants eventually enrolled (the reasons given for non-participation of the others were recorded)

and this sample were described as consistent with the haemophiliac population of the USA (Stehbens *et al,* 1997, p. 125). There were no significant differences between the HIV positive and HIV negative groups on the socio-economic and ethnicity variables.

Sirois *et al* (1998) reported that a further 35 participants were excluded from the analysis because they failed to complete all elements of the assessment. All N = 298 participants were males with moderate to severe haemophilia and fluent in English. All participants were born between 9th January 1970 and 9th January 1982, they were probably exposed to HIV infection between 1978 and 1985.

The reports differ slightly on the numbers of participants in each study group:

Loveland *et al* (1994) and Stehbens *et al* (1997) discussed the n = 207 HIV positive participants and the n = 126 HIV negative participants at the study baseline.

Stehbens *et al* (1997) also reported that there was a significant age difference, the HIV positives were around two years older (mean averages: 13.1 years and 11.2 years respectively). This proportion reflects the greater number of severe haemophiliacs in the sample and age will be used as a control variable as appropriate. The estimated mean time elapsed since infection was 6 years. [Stehbens *et al,* 1997]

Sirois *et al* (1998) reported that the participants were grouped in three categories:

- n = 120 HIV negatives (40.3%);

and a total of n = 178 HIV positives grouped as follows:

- n = 128 HIV positives with CD4 > 200 (42.9%); and
- n = 50 HIV positives with CD4 < 200 (16.8%).(immune compromised)

Those with more severe haemophilia were more likely to have become HIV positive due to more frequent exposure to factor concentrate.

Sirois *et al* (1998) also reported the baseline data recorded between March 1989 and June 1990. The participants were then aged 7 – 19 years. The HIV positives were older by a statistically significant margin ($p < 0.0001$), the group mean ages were HIV Positives = 13 years and HIV Negatives = 11 years.

It is possible to criticise this large study for not having a non-haemophiliac control group, as have been recruited in some other studies (it has been confirmed that they will add such a control group). However the HGDS is the largest available study of young haemophiliacs with and without HIV infection and is therefore valuable even without that control group.

HGDS hypotheses

Loveland *et al* (1994) described the null hypotheses being tested by HGDS as follows:

1. *HIV+ subjects are no more likely than HIV– subjects to have lowered neuropsychological performance in three or more of the areas of functioning examined.*
2. *Neuropsychological test scores of HIV+ and HIV- subjects do not differ significantly.*
3. *Absolute CD4 cell count per mm^3 is not related to neuropsychological performance in either HIV+ or HIV- subjects.*

HGDS findings

Loveland *et al* (1994) [first report from the HGDS] reported that at baseline two participants from the HIV positive group and two from the HIV negative group were excluded because the examiners believed the data they provided was invalid. Therefore the final sample size was 205 HIV+ and 124 HIV- cases drawn from 14 Hemophilia Treatment Centers. Very few of these cases met the CDC criteria for AIDS, but 65/204 (31.9% were taking AZT at entry into the study. At baseline the HIV positive participants were estimated to be 4 - 7 years post-infection and were significantly older than the HIV negative participants (13.14 and 11.17 years respectively) and they were more likely to have had remedial education at some point . The HIV positives also had significantly lower CD4 counts: 61.8% of the HIV positive group and 10.5% of the HIV negative group had CD4 below 500/mm^3.

The HGDS planned for multi-centre evaluations by shared training session for all psychologists involved in the project and by developing a joint procedures manual and standardised test administration in terms of both order and approach (emphasis on establishing rapport and maintaining child co-operation). The psychologists used a standardised rating scale to record their own impressions of the validity of each child's assessment and only those judged valid were analysed.

The collection of prior medical history data proved difficult, with basic documentation missing in many cases (e.g. birth weight was not available in 25% of cases). At baseline, as one might expect, the HIV positives had lower CD4 counts than the HIV negatives, though the HIV positive group mean was 420 (with Std. Dev. = 319), which is within the mild to moderate immune compromise range[20]. The HIV negatives' mean CD4 was 956 (with Std. Dev. = 380).

There were some differences between the HGDS study groups in terms of developmental / educational history in that the HIV positives were more than twice as likely as HIV negatives to have been enrolled in some form of remedial special education; whereas a history or being slow to walk or slow to speak was more likely in the HIV negative group.
On all other measures (e.g. presence of dyslexia, Attention Deficit / Hyperactivity Disorder, Conduct disorder, depression) the two groups were similar.

[20] normal CD4 = 500+/mm^3 ; mild to moderate compromise 200 – 499/mm^3; below 200/mm^3 severe compromise leading to AIDS diagnosis.

Loveland *et al* (1994) reported no effects of HIV infection on neuropsychological performance at baseline. Subtle deficits relative to age norms were seen in *both* HIV + and HIV- children with haemophilia and Loveland *et al* suggested that the direct consequences of haemophilia itself may affect cognitive development.

Loveland *et al* (1994, p. 229) reported that:

> *"when mean scores were adjusted for the co-variates included in the final models, there were no statistically significant differences between the HIV positive and HIV negative groups in the neuropsychological outcome variables. There were also no relationships with CD4 cell numbers."*

The performance of both the HIV positive and HIV negative groups in all neuropsychological domains was average to above average relative to published test norms. However there were some unexpected profiles of test performance across both study groups: for example the adjusted mean standard scores for academic achievement and adaptive behaviour were 10-15 points lower than one would expect based on the mean Full Scale IQs. Both groups' parents reported more health problems and more cognitive concerns than would be expected for the general population.

However Loveland *et al* (1994) did note some interactions which led to the identification of significant relationships with HIV status in sub-groups of the sample, see below. They selected ($p < 0.01$) as their criterion for statistical

significance, but they have reported a trend where the probability was ($p \leq 0.05$).

Interactions within neuropsychological domains between HIV status and other variables (variables which are not neuropsychological tests are indicated by *italic text*):

General intelligence: produced an interaction between HIV status and the presence / absence of an *estimated SEI* (Estimated Socio-economic Index) score (there were no *SEI* norms to provide a score for those reporting "homemaker" as head of household and an estimate was applied based on the parent's level of education). Where *SEI* was estimated, FSIQ was significantly ($p \leq 0.005$) lower in HIV positive than HIV negative participants. There was no such relationship for those for whom the *SEI* was not estimated.

Memory: Wechsler Digit Span and Information sub-test scores were significantly ($p \leq 0.01$) related to *SEI, being in a "gifted" class,* and *repeating a grade.* In addition the Wechsler Information score was positively related to *parental education*. The Rey AVLT was negatively related ($p \leq 0.01$) to *being in special education* and *having repeated a grade*.

Language: in this functional area there was a relationship *between factor level (severity of haemophilia)* and *HIV status*: for participants with mild/moderate haemophilia the Wechsler Comprehension and Vocabulary sub-scores were significantly ($p \leq 0.01$) higher in HIV negative than HIV

positive participants. For those with severe haemophilia, the HIV negatives had significantly greater scores in Word Fluency (FAS) than HIV positives.

For severe haemophiliacs most of the language tests (Wechsler Similarities, Comprehension and Vocabulary, plus Word Fluency and Boston Naming) were significantly related to *"age squared", SEI, being in a "gifted" class*, and *repeating a grade*. For mild-moderate haemophiliacs there were fewer relationships but most tests were related to *being in a "gifted" class*.

Visual Spatial: most tests in this domain were related ($p \leq 0.001$) to *SEI, repeating a grade* and *being slow to walk.* In addition the VMI and Line Orientation were each related to *age*.

Fine Motor: The Wechsler Coding sub-test and Beery VMI each showed a significant ($p \leq 0.01$) relationship to *repeating a grade*. The VMI was also related ($p \leq 0.05$) to *having been in a special education class*, and the presence of an *estimated SEI* was related ($p \leq 0.05$) to the Grooved Pegboard Dominant Hand Score.

Academic: for this functional area there was an interaction between *age* and *HIV status*. When the sample was age grouped (6 - 8; 9 -11; 12 -15; 16 -19 years) the effect of HIV status approached significance for WRAT-R Reading ($p \leq 0.02$) and WRAT-R Arithmetic ($p \leq 0.03$). However, examination of the adjusted means indicates that this difference is in the opposite direction to that which was expected (i.e. HIV positive participants tended to have higher

academic scores than HIV negative participants, particularly in the older age groups).

The effects of the other co-variates were similar across age groups, with *SEI*, *being in a "gifted" class* and *repeating a grade* being related ($p \leq 0.05$) to some or all of the academic component tests across all age groups. In addition (for the oldest group only) *being in a special education class* was significantly negatively related ($p \leq 0.01$) to all three academic component tests.

Adaptive Behaviour: *Having repeated a grade* and *being in a "gifted" class* were each positively related to Adaptive Composite score and the Communication domain ($p \leq 0.001$) and approached significance ($p \leq 0.05$) in the Daily Living domain. *Repeating a grade* was negatively related to the Socialisation domain. *Age* was significantly related ($p \leq 0.01$) to the Socialisation domain and approached significance ($p \leq 0.05$) with the Communication domain.

Attention / Concentration: All three component tests of the Attention / Communication domain were positively related to *SEI* and negatively related to *repeating a grade* ($p \leq 0.01$). The Wechsler Arithmetic sub-test (only) was related to *being in a "gifted" class*.

Emotional / Behavioural: four of the five factors of the Pediatric Behavior Scale ("Conduct", "Attention Deficit", "Depression-Anxiety" and "Deviation") were significantly related to *age* ($p \leq 0.001$) with the parents of older

participants tending to report more problems. In addition "Deviation" was related to *repeating a grade* and "Health" was related to *estimated SEI* score.

After the final set of co-variates were entered into the Loveland *et al* (1994) regression model, the following tests and sub-tests were related to *age* or to *age squared*: see Table 1.4.3.5C.

Tables 1.4.3.5C: Summary of baseline results of the HGDS Loveland *et al* (1994)

Tests related to *age*	**Tests related to *age squared***
Rey AVLT	Rey AVLT
Boston Naming Test	Boston Naming Test
FAS Word Fluency	FAS Word Fluency
Benton Line Orientation	Grooved Pegboard Dominant Time raw scores
Grooved Pegboard Hand Time	Wechsler Similarities and information sub-tests
Pediatric Behavior Scales (PBS: "Conduct", "Attention Deficit", "Depression-Anxiety" and "Deviation" sub-scales)	
Vineland Socialisation domain standard / scaled scores	
Beery VMI	
Wechsler Similarities sub-test	

Poorer performance associated with increasing age was observed for all of the (above) standard / scaled scores which were related to age or age squared which, for Loveland *et al,* suggested that older participants were performing less well compared to younger participants. In contrast for raw scores (above), which were related to *age* or *age squared,* increasing age

was associated with higher scores. With the exception of the PBS scores this reflects the normal increase in skills during development. For the PBS this reflects greater numbers of behavioural / emotional problems reported by parents for older participants.

Loveland *et al* (1994) also reported the number of "outliers" (scores more than 2 standard deviations from the sample mean in the direction of poorer performance) for each neuro-psychological test. Overall 27% (N = 88) participants had one or more scores which met this criterion. There was no difference between the HIV positive and HIV negative groups in the percentage of outlier scores.

Loveland *et al* (1994) noted that for those on AZT treatment (32% of HIV positives at baseline) when using age as a co-variate, only the PBS "Cognition" factor differentiated between those who were and were not on AZT ($p \leq 0.01$). Parental reporting gave those on AZT an average PBS "Cognition" factor score of 7.2, which compared to a mean of 4.0 for those not on AZT. The "Depression / Anxiety" factor showed a similar trend: those on AZT had higher scores ($p \leq 0.03$) indicative of more depression and anxiety in this group. However such scores must be interpreted with caution as those on AZT were not selected at random and there is also a possible effect of the medication.

Loveland *et al* (1994, p. 235-6) summarised the main findings of the baseline assessment:

"At baseline the HIV+ and HIV- groups enrolled in the HGDS did not differ in overall neuropsychological performance or in the number of individuals showing below-average performance in several areas".

"At the same time, a greater than expected number of individuals in both groups showed below average performance, and the groups as a whole had lowered performance in adaptive behavior and academic achievement measures, relative to IQ."

These findings are consistent with those of Whitt *et al* (1993) and suggest that haemophilia itself may account for the below average performance of about 25% of all participants, in both groups, perhaps as a result of repeated school absences and treatment. This emphasises the need for appropriate control groups for all studies of HIV disease. In addition other non-HIV psycho-social factors are likely to have a role in mediating the effects of HIV and so one must also check these variables for significant effects. Loveland *et al* (1994) did not mention a possible selection bias: it is feasible that those families volunteering to participate in research are more concerned about learning or behaviour problems in their offspring, so sibling and non-haemophiliac controls are also essential.

"Absolute CD4 counts per mm^3 were not related to neuropsychological performance in either the HIV+ or HIV- group".

Loveland *et al* (1994, p. 236)

This finding is consistent with other studies of asymptomatic young men (e.g. Whitt *et al,*1993; Karlson *et al,*1993), though some researchers (e.g. Bornstein *et al,*1991) have suggested that the rate of change in CD4 cell numbers rather than absolute counts may be related to neuropsychological performance.

> *"The baseline findings indicate that the young HIV+ [participants] were relatively free of HIV encephalopathy 4 or more years after seroconversion".* Loveland *et al* (1994, p. 236)

> *"The progression of HIV related brain disease in pediatric patients who became infected past infancy may resemble the lengthy course seen in adults more than the relatively rapid course seen in some cases with congenital HIV infection (Tovo et al,1992). However the lack of HIV-related deficits at baseline in this sample does not rule out the possibility that sub-clinical impairments are present in areas such as attention and speed of information processing, which have been found to be impaired in some HIV+ patients without AIDS tested with specialized computer-based measures (e.g. Wilkie et al,1992). "*
> Loveland *et al* (1994, p. 236)

Sirois *et al* (1998) applied a "least squares" modelling from standard (or age scaled) scores and found that the majority of participants had achieved major developmental milestones (e.g. speech and walking) within age expectations. Seizures (≤10%) and neurological infections other than HIV (≤ 6%) were observed infrequently. A proportion of each of the three groups had a history

of gait disturbance (10 – 15%) and intra-cranial haemorrhage (4 -12%). Prior history of head [21]trauma (36% to 41.5%), academic[22] difficulties (26% to 36.8%) and prior diagnosis of psychological[23] dysfunction (24% to 36.8%) were relatively common in all groups of participants (note that the ranges given are for all three groups merged together).

On MRI scan the majority of abnormalities identified were due to diffuse cerebral atrophy, though some other pathologies (congenital abnormalities, old hemorrhagic lesions and focal atrophy) occurred infrequently.

Sirois *et al* (1998) noted that it was particularly striking that the rates of academic difficulties, psychological dysfunction and various aspects of neurological impairment were not zero for the HIV negative control group. In fact for *"previous Intra-cranial haemorrhage", "previous head trauma"* and *"pre-existing gait disturbance"* the HIV negatives' rate was higher than that of either HIV positive group. Researchers have often assumed that haemophiliacs without HIV infection have no other difficulties: this study provides evidence to the contrary. *Sirois et al* (1998) therefore highlighted the importance of prompt diagnosis and treatment of general haemophilia-related problems.

[21] Documented in medical records.
[22] Sirois *et al* (1998, footnote p.49) report that this was *"defined as either having repeated a grade in school of current placement in a remedial special education class".*

[23] Sirois *et al* (1998, footnote p.49) report that this included: *"previous diagnoses of learning disability / dyslexia, attention deficit / hyperactivity, developmental language delay, conduct disorder / oppositional, depression, personality disorder, eating or sleeping disorder, enuresis / encopressis, and motor impairment."*

The neurological findings reported by Sirois *et al* (1998) were much as expected:

- the two HIV positive groups were each more likely to *have abnormal or equivocal appearance on MRI* than the HIV negatives: those with CD4 < 200 ($p < 0.001$) and those with CD4 $\geq$ 200 ($p < 0.006$).

Note: once again the HIV negatives did not have a zero rate of abnormality.

- the HIV positives were also more likely to display *diffuse cortical atrophy*: both groups ($p < 0.0001$).

However:

- *decreased muscle bulk (not associated with a damaged joint)* was limited to those with CD4 < 200 ($p < 0.02$), those with higher CD4 counts did not differ from the HIV negatives.
- *Co-ordination and / or gait abnormality* was typically associated with haemophilia, rather than HIV infection, since it was more prevalent in the HIV negative group [28% versus 21% (CD4 < 200) and 24% (CD4 $\geq$ 200)].
- *Reflexes and cranial nerve function and baseline EEGs* were normal in over 90% of the sample, regardless of HIV status.

Sirois *et al* (1998) reported the neuropsychological findings: the functional areas considered were labelled *general intelligence, language, memory, attention, academic , visual spatial, fine motor, adaptive behaviour, behavioural-emotional.*

- In general the participants were achieving at the appropriate level for their age on the measure of *general intelligence*.

- HIV status was not related to neuropsychological performance at baseline.

However

- there were significant differences in *general intelligence,* regardless of HIV status, as measured by the Wechsler Full Scale IQ where academic problems ($p < 0.001$) or previous head trauma ($p < 0.003$) were present.

- Differences in performance on the Wechsler summary scores were also apparent where there was co-ordination and/or gait abnormality ($p < 0.001$ for FSIQ).

- Sirois *et al*'s (1998) least squares analysis determined the statistically significant ($p \leq 0.05$) co-variates for each functional area. These are summarised in the table below, with the areas in which they were significant.

- A history of academic problems (defined as having either repeated a grade in school or current placement in a remedial special education class) was related to problems in all neuropsychological function areas except parental reports of "behavioural / emotional" difficulties.

- The parents' level of education was related to their child's performance in all areas except "fine motor" and "behavioural / emotional".

- A history of head trauma was related to performance in the General Intelligence, Language, and Visual-spatial areas.

- Prior diagnosis of psychological dysfunction was related only to parental reports in the Behavioural / Emotional area.

The final stage of the Sirois *et al* (1998) analysis was to identify significant ($p \leq 0.05$) interactions between the neurological findings and the co-variates by neuropsychological function area. The significant interactions are summarised in the table below.

Tables 1.4.3.5D
Summary of HGDS findings as reported by Sirois *et al* (1998)

Hemophilia Growth and Development Study:	**Neuropsychological Functional Area**				
Interaction * indicates a significant interaction ($p \leq 0.05$) between the neuropsychological functional area and the neurological findings.	General intelli-gence	Language	Memory	Acad-emic	Behav-ioural / emot-ional
MRI general appearance x co-ordination and / or gait abnormality	*		*		
MRI diffuse atrophy x co-ordination and / or gait abnormality	*		*		
MRI diffuse atrophy x parents' education		*		*	
Increased reflexes x parents' education	*				
Decreased muscle bulk x head trauma	*				
Cranial nerve abnormality x co-ordination and / or gait abnormality			*		
Cranial nerve abnormality x age					*
HIV category x prior diagnosis of psychological disorder					*^

^ the range of scores on this parental report measure of behavioural / emotional difficulties was so narrow that the differences were described as not clinically meaningful.

In terms of the HGDS hypotheses, Sirois *et al* (1998) found that:

Hypothesis 1 concerning neurological and neuropsychological impairments, was partially supported. The HIV positive participants with lower CD4 counts showed more impairment than did HIV negative participants (and those who were HIV positive with CD4 count above 200), but only on the MRI studies.

Hypothesis 2 concerning poorer neuropsychological performance for those with neurological exam abnormalities regardless of HIV status, was also partially supported. Neuropsychological performance was significantly lower for participants who showed abnormalities on the neurological examination relative to those who did not, regardless of HIV status, but only for those showing co-ordination / gait abnormality, not for other neurological variables.

Hypothesis 3 (interactions) was partially supported. Interactions among the HIV, neurological and environmental variables, when analysed together, revealed patterns of influence on neuropsychological performance. However these interactions indicate that, at least in the asymptomatic phase, people with haemophilia are relatively resilient in terms of neuropsychological functioning.

In addition to their primary hypotheses, Sirois *et al* (1998) noted that a number of the more subtle effects demonstrated in their study are actually linked to haemophilia, rather than to HIV infection. They emphasised the importance of prompt treatment of bleeds, prophylactic therapy as appropriate and regular neuropsychological monitoring as part of the standard care package for people with haemophilia.

Sirois *et al* (1998) discussed various issues, including whether the tests they used were sufficiently specific and sensitive. Certainly post-mortem and radiological studies indicate relative sparing of the cortex and extensive sub-cortical pathology. The neuropsychological tests selected (here and in other studies) are sensitive largely to cortical functioning rather than sub-cortical activity. They also speculate whether the "CD4 count of 200+" threshold is sufficient to identify those with the most severe immune compromise.

Sirois *et al* (1998) also discussed whether their results can be interpreted in terms of a "percolation theory", which suggests that changes will become apparent only once some critical threshold of neural damage is reached (Nadel, 1990). It is apparent that the Sirois *et al* (1998) study cannot fully answer this question, though it contributes data which suggest that cognitive performance may be lowered as a result of a combination of neurological abnormalities and environmental conditions. Further studies considering performance in relation to the timing of illness or death will be required.

Sirois *et al* (1998) considered the possibility, raised by Sameroff and Chandler (1975), that environmental factors (e.g. supportive home) may maintain cognitive stability, even in children with early brain damage. Sirois *et al* (1998) commented that parental education was related to cognitive performance and that this sample may therefore have lived in "relatively privileged circumstances", Sirois *et al* (1998, p.53). However this comment has not been expanded with a more detailed investigation of the potential social environmental issues.

Sirois *et al* (1998) also considered the possibility that some developmental factors may have been protective, due to the age at infection of the participants in their study. Longitudinal investigation of those infected by transfusion (Eyster, 1991) indicated that progression to AIDS was slowest in those aged 1-18 years, compared to those infected at younger or older ages. Ehmann *et al* (1994) even demonstrated that survival rates were greater for those haemophiliacs infected in this age group *regardless* of their CD4 counts.

Sirois *et al* (1998) therefore concluded that their sample were typical of the haemophilic / transfusion "risk group" in having normal cognitive performance whilst relatively healthy (seven years post-infection on average at study baseline). This pattern is very different from those infected vertically, who typically have a rapid decline in functioning.

Stehbens *et al* (1997, p.128) summarised the HGDS findings reported by Loveland *et al* (1994) thus:

> *"The general functioning of the HIV positive and HIV negative groups did not differ in overall neuropsychological performance, but both groups had below-average performance in academic achievement and adaptive behaviour relative to IQ. There were clear associations between socio-economic status, parental education, educational history and neuropsychological performance, suggesting that non-HIV-1 psychosocial variables underlie patterns of test performance."*

Stehbens *et al* (1997, p. 128) drew a more general conclusion:

> [The findings] *"...suggest that HIV-1 disease in post-natally infected children resembles the lengthy course seen in adults more than it does the relatively more rapid course with some congenitally acquired HIV-1 infections (Tovo et al,1992)."*

Bordeaux et al (2003) reported on the HGDS parents' views: those with HIV positive children (and especially those developing immune compromise) perceived greater psychosocial problems. Those with sons who were immune compromised reported more health concerns (such concern would be realistic in those circumstances); greater social withdrawal; physical and adaptive limitations associated with illness; greater concern about their sons' health and greater pessimism about their sons' futures (again such concerns appear realistic); as well as poorer family integration and more limited family integration.

Stehbens *et al* (1997) also addressed some of the key questions and implications for practice raised by the HGDS:

- ***Can neurodevelopmental problems precede the symptomatic stage of HIV disease in children infected past the peri-natal period?***

  Stehbens *et al* (1997) report that this question is controversial in the adult literature and remains unanswered for children and adolescents: group based studies have so far not shown any group differences, but longitudinal analysis of the disease trajectory in individual children will be required to answer this question.

- ***What relationships (if any) exist between immunological variables and disease progression in children and adolescents with haemophilia and HIV-1 infection? ?*** Stehbens *et al* (1997) reported that the natural history of HIV disease in those infected post-infancy is poorly understood and the question of a specific relationship between plateaux and declines in neurobehavioural functioning and immune function will be of particular interest. Some recent studies (e.g. Karlsen, Reinvang and Froland, 1993; Loveland *et al,*1994; Whitt *et al,*1993) have not found relationships between CD4 counts and neuropsychological functioning. Stehbens *et al* (1997) added that differences in age at infection and in haemophilia-associated illnesses and treatments are likely to be factors in this population. E.g. those with severe haemophilia who have received a higher number of factor treatments are at increased risk for other serious infections such as hepatitis B or C which could also affect neurodevelopmental variables. Similarly, haemophilia-associated joint disease may affect gross or fine motor performance.

- ***What relationships (if any) exist between / among EEG, MRI and neurological examination findings and neurobehavioural functioning in children and adolescents with haemophilia, with and without HIV-1 infection?*** Stehbens *et al* (1997) reported that such relationships are incompletely understood as yet. Longitudinal studies involving such careful and detailed evaluations will be required to address such questions. Some recent studies (e.g. Brouwers *et al,*1995; DeCarli,

Civitello, Brouwers and Pizzo, 1993) suggest that there may be differing patterns of brain changes in those infected vertically and those infected through transfusion.

- ***Are neurobehavioural deficits more likely to occur in HIV negative children and adolescents with haemophilia than in their non-haemophiliac male siblings?*** Stehbens *et al* (1997) reported that the HGDS will address this issue by inclusion of a sibling control group.

Summary:

Researchers (e.g. Belman, 1997) agree that the results from studies of neo-nates and infants cannot be generalised to people infected later in childhood or in adulthood because of the probability that the HIV will have different effects on the brain at differing stages of its development.

It is clear from a range of studies (e.g. Navia *et al*, 1986; Kaslow & Francis, 1998) with participants from a range of groups (e.g. those infected vertically, through IV drug use, homosexual behaviour, etc.) that people with HIV related illness which has reached the symptomatic stages can experience neuropsychological dysfunction. That dysfunction is unpredictable, it can range anywhere from minimal to global in its effects and occurs in both adults and children. There is no one pattern of neurological disease progression and psychiatric symptoms are also variable. In the recent research there appears to be a reasonable degree of consensus (e.g. McArthur, 1989; Belman *et al,* 1988; Riccio *et al,* 1988) that such dysfunction may result either from indirect

effects (e.g. opportunistic infections) or from the direct effects of the HIV. The likely mechanism for this damage is that the virus crosses the blood-brain barrier relatively early in the disease course. It then attaches to CD4 receptors on various brain cells and damages those cells, the precise mechanism of such damage is not yet fully understood.

The literature remains inconclusive on the question of whether or not there are subtle but measurable cognitive changes in the earlier, asymptomatic, stages of HIV infection. The results of the Grant *et al* (1987) study have not been consistently supported in subsequent studies of people at the asymptomatic stages of infection.

Study hypotheses

The hypotheses to be tested were:

Hypothesis 1 (psychiatric assessment):

$H_{1\,E}$: The HIV Positive group will produce a significantly higher proportion of participants who meet the criteria for a "psychiatric case" at each of the annual assessments than the general population.

$H_{1\,0}$: *There will be no significant difference between the proportions of the HIV positive group and general population who meet the "psychiatric case" criteria at each of the annual assessments.*

Hypothesis 2
(cross-sectional analyses of the neuropsychological key variables)

$H_{2\,E}$: The HIV Positive group will produce poorer performance (by a statistically significant margin) on each of the 19 key neuropsychological variables compared to the control groups at each of the annual assessments.

$H_{2\,0}$: There will be no statistically significant difference between the performance of the HIV Positive group and the performance of the Control groups on any of the 19 key neuropsychological variables at any of the annual assessments.

Hypothesis 3 (longitudinal analyses of the neuropsychological key variables)

$H_{3\,E}$: The HIV Positive group will show a statistically significant decrement in their performance over time (comparing Assessment 1A to 3A) for each of the 19 key neuropsychological test variables. The HIV Negative and Non-haemophiliac Control groups will not show a decrement in performance over time on the key neuropsychological variables.

$H_{3\,0}$: There will be no statistically significant change in the performance over time of the HIV positive group (comparing 1A to 3A assessment) on each of the 19 key neuropsychological variables.