AIDS/HIV

The effects of infection with HIV, including the effects of treatment, on patients and their families.- A report prepared for the Penrose Inquiry by CLS Leen 8 June 2011

The treatment and care (i.e. medication, counselling and any other holistic care) which has been given to patients in Scotland since the virus was discovered, including the use of drug trials

In the early 1980s, patients had HIV related conditions and these were managed with the appropriate treatment at the time. If this was thrush, it would have been an antifungal drug; if pneumonia, an antibiotic; if a viral infection with Herpes simplex or herpes zoster or cytomegalovirus, an antiviral treatment etc. There is a whole list of HIV related conditions and specific treatment would be directed at these conditions. One relatively common condition is thrombocytopenic purpura for which intravenous immunoglobulin was prescribed. In the early 1980s, when an HIV infected patient was diagnosed, this patient may well have been cared for the physician who made the initial diagnosis. It could be a haematologist, a Genito-urinary medicine doctor, a gastroenterologist, a respiratory physician or an infectious diseases physician. Referral patterns depended a lot on whether the physicians had any interest in HIV/AIDS locally or regionally. This would have probably been the case until the mid 1990's. In Edinburgh, one of colleagues held joint clinics with the haemophilia doctors in the haemophilia centre in order to keep clinic visits to a minimum for the haemophilia patients. It is quite likely that similar joint clinics were held in other parts of Scotland.

From the mid 1990's onwards HIV infected patients would be referred to either the Infectious Diseases Unit or to the Genito-urinary Medicine Department nearest to them. Following diagnosis, they will be offered a full

assessment by an HIV specialist and they will also be offered psychological support by a counsellor or a psychiatrist if needed.

Treatment is usually for the HIV and for any other concomitant condition which is associated with their HIV infection. Such conditions may include opportunistic infections or cancers and may also include AIDS defining conditions. Inpatient HIV treatment is usually delivered by Infectious Diseases Units in Scotland.

The first consensus statement on HIV treatment was issued by a panel of US experts following a State-of-the-Art Conference on Azidothymidine Therapy for Early HIV Infection. This conference was sponsored by the National Institute of Allergy and Infectious Diseases (US National Institute of Health) in 1990. The panel concluded that a large proportion of the asymptomatic and mildly symptomatic HIV- infected population were candidates for early therapy with zidovudine. This was followed by updates in 1993, 1996.

The US Department of Health and Human Services has also produced Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents since 1998 and these are regularly updated on a yearly basis.

The first British Consensus statement on the treatment of HIV appeared in April 1997 in the Lancet and was revised very quickly in 1998. Since then British guidelines have been updated or rewritten in 2000, 2001, 2003, 2005, 2006, 2008. In 2011, new guidelines for HIV treatment will be issued by the British HIV Association.

How did clinicians determine treatment before there were guidelines? How did they determine treatment in the 1980s, including how did they decide when to start treatment?

Prior to the advent of guidelines, clinicians would treat AIDS patients with Zidovudine or any licensed drug that was available. What was used would largely depend on the clinical experience of the prescribing physician and on

how up to date he/she was and whether the unit caring for the patient had access to clinical trials of new anti-HIV drugs. Between 1987 and 1993, two additional HIV drugs (didanosine and Zalcitabine) were undergoing clinical trials. HIV physicians had to wait until 1993 when a State of the Art Conference reviewed the use of anti-retroviral therapy in Adult HIV infected patients in the US. Advice on using CD4 cell count and clinical assessment to monitor disease progression was formulated. These included when to initiate treatment for patients depending on their CD4 cell count or on whether they were symptomatic or not and also when to change treatment from zidovudine to didanosine.

There was controversy surrounding when and what HIV treatment should be initiated in asymptomatic HIV positive patients. Clinical trial results informed clinicians about when to initiate treatment and what drugs to use. National guidelines were formulated after consensus was achieved following close scrutiny of trial results.

Treatment for their HIV is started when patients have symptomatic HIV disease and if asymptomatic treatment will be started according to their CD4 cell count and based on the British HIV Association HIV treatment guidelines. The first UK national HIV treatment guidelines was formulated in 1997 by the British HIV Association (BHIVA). The guidelines recommended starting HIV treatment when the CD4 cell count fell below 300 cells μL and also recommended possible combinations of anti HIV drugs to use.

Patients may also be offered the opportunity to take part in HIV clinical trials available at the time. In Edinburgh, patients would have had access to most of the HIV drug trials since 1985. These clinical trials include those funded and run by the Medical Research Council, as well as those run by the Pharmaceutical Industry to demonstrate efficacy of new drugs in order to obtain a licence for their use. I cannot comment on access to clinical trials in other centres in Scotland. There is a very formal process for initiating and performing clinical trials in the UK; ethical approval, Trust or Health Board management approval were required before patients could be entered into

the clinical trial.

Was there a time when a clinical trial was the only option available to patients with HIV?

In the early years, before the advent of triple HIV therapy , the so called HAART (Highly Active Anti- Retroviral Therapy) era, it is quite common for patients to develop progression of their HIV disease despite HIV treatment. Treatment with a single HIV drug led to a short lived improvement in the patient clinical condition. Later we came to understand that resistance to the HIV drug developed very rapidly when single drug was used, less rapidly when 2 drugs were used. The use of triple HIV combination (HAART) led to sustained suppression of HIV replication. This then allowed the immune system to reconstitute and as a consequence marked and sustained clinical improvement was expected. With full suppression of HIV replication, there is negligible HIV replication and HIV drug resistance did not emerge.

In the early years, patients with advanced HIV disease were treated with whatever drug was available. These drugs were either (a) licensed for use or (b) were available on a named patient programme (Expanded access programme) or (c) only available as part of a clinical trial. Patients can access an unlicensed drug through a clinical trial before that drug would be available through a named patient programme and also before the drug would be licensed by the regulatory authorities. Sometimes, the drug was not shown to be effective enough to be licensed. Drugs that were tested but did not progress to licensing include, loviride, capravirine, vicriviroc .

Some patients who could not or did not want to wait for the drug to be licensed would then consider the clinical trial or named patient programme options. There are strict inclusion and exclusion criteria for clinical trials and some patients were too ill and were therefore excluded from trials.

We have learned a lot about clinical trial design. How would we test the efficacy of one drug when it is one component of a combination regimen of

three drugs? How do we test the efficacy of new drugs in patients with HIV drug resistance without limiting future options for the patient, when adding a single drug to a failing regimen would mean that the benefit of the new drug may only be transient?

Were there clinical trials of treatment for HIV in Scotland which subsequently were unsuccessful?

Although some studies did not benefit all patients, they informed future treatment strategies. Concorde was a European trial of immediate zidovudine vs deferred zidovudine (500 mg twice daily) in asymptomatic patients (Medical Research Council/Association Nationale de Recherche du SIDA, 1993). No difference in survival or progression to advanced disease was seen after a mean study period of 3 years in the subset of 710 patients with entry CD4+ cell counts greater than $0.50X10^{7}L$. This study demonstrated that zidovudine monotherapy did not benefit patients with high CD4 cell count. Subsequent studies showed that taking 2 anti HIV drugs was better than taking a single drug and that taking a combination of three drugs was better than taking 2 drugs.

The SMART study showed an excess risk of Cardiovascular disease among patients receiving intermittent ART. The results of the SMART study would also support the recommendation that total treatment interruption cannot be recommended in the management of the treatment-experienced patient.

So not all studies benefitted all patients but a lot was learned from these studies and they improved subsequent patient care.

The 1998 revision of the 1997 BHIVA HIV treatment guidance stated that a combination of 2 nucleoside analogues was no longer considered a reasonable standard of care and therefore should only be considered in very exceptional circumstance. Therefore from 1998 onwards, 3 drugs will be

chosen from the list of preferred options. This choice is informed from the patient's lifestyle, risk factors for other co-morbid conditions. The regimen is chosen to fit the patient's daily routine to ensure near perfect adherence and to ensure that any likely side effects would be tolerated by the patient.

Studies have reported that 90%–95% of doses must be taken for optimal suppression, with lesser degrees of adherence being associated with virologic failure (Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133:21-30). Predictors of optimal adherence to HIV medications, and hence, optimal viral suppression, include 1) availability of emotional and practical life supports; 2) a patient's ability to fit medications into his or her daily routine; 3) understanding that suboptimal adherence leads to resistance; 4) recognizing that taking all medication doses is critical; 5) feeling comfortable taking medications in front of others; and 6) keeping clinic appointments.

Adherence support is given to the patient by a team of clinical nurse specialist, dietician, doctor, and counsellor. The patient will be supported by a Social Worker for advice regarding social and housing benefits. Between 1996 and 1997 when we saw that patients were struggling with their complex medication regimen, we built the adherence support team in the Regional Infectious Diseases Unit in Edinburgh. By 2001, BHIVA issued guidelines on adherence.

The developments/changes in treatment for HIV and AIDS over the years.

In 1987, Zidovudine was the first HIV drug approved for use in patients with AIDS. In a double blind placebo controlled study of zidovudine in patients with AIDS or AIDS related complex, 19 patients on placebo versus 1 patient on zidovudine died during 6 months study, and the rate of opportunistic infections was also statistically significantly reduced in the zidovudine arm.

While there were more drugs approved for use in HIV, we were aware of the limitations of using a single drug (resistance documented after zidovudine monotherapy in 1989) or even a combination of 2 drugs (1997 Treatment guidelines).

When the licensed drugs lost their efficacy because of the emergence of drug resistance, patients became symptomatic and developed further opportunistic infections. Many were desperate to try anything to keep them alive. Intravenous immunoglobulin treatment has been widely used to treat Idiopathic Thrombocytopenic purpura in the general population as well in those who are HIV infected. In children, there has been some positive experience with using immunoglobulin treatment and while I have used this treatment for HIV infected individuals with recurrent bacterial pneumonia and in HIV infected patients with severe parvovirus infection, it is quite possible that other HIV specialists may have used it to delay HIV progression in HIV infected adults. However, current Highly Active Anti-Retroviral Treatment is extremely effective, current practice does not include the use of intravenous immunoglobulin in HIV infection except for severe parvovirus infection and rarely intractable thrombocytopenia.

Hydroxyurea, an inhibitor of DNA synthesis, has been used to treat HIV infection. By inhibiting ribonucleotide reductase, hydroxyurea depletes the pool of deoxynucleoside triphosphates, particularly dATP, available for DNA synthesis. This was used for a limited time before 1997 but is associated with significant toxicity and has not been approved by the FDA. Better and more effective drugs are now available.

Often patients were prepared to endure quite significant side effects. Eventually, after long periods of fighting the disease and when they realised that their quality of life had been eroded, efforts were concentrated on improving and maintaining what was left of their quality of life. Often, because the drug(s) lost their benefit, a positive decision would be taken with the patient to stop any intervention that was unlikely to benefit the patient or

had any side effects. Decision about of end of life care and management would be agreed with the patient and his or her loved ones.

In 1996, the availability of availability of new sensitive laboratory techniques made possible the confirmation of the very dynamic role of HIV at all stages of the disease. The daily turnover of HIV was been estimated to be at least 10^{10} viral particles, similar to the CD4 cell turnover. It was now clear that CD4 cell destruction occurs as a result of HIV replication.

It was not until 1996 that we witnessed a marked improvement in the efficacy of anti HIV drug treatment. A new class of drugs (Protease Inhibitors) was shown to dramatically suppress HIV replication, leading to marked improvement in clinical outcome.

In 1996, five large randomised clinical trials (1. Saravolatz LD, et al. Zidovudine alone or in combination with didanosine of zalcitabine in HIV-infected patients with the acquired immune deficiency syndrome or fewer than 200 CD4 cells per cubic millimeter. N Engl J Med 1996; 335: 1099–106.; 2. Hammer SM, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200–500 per cubic millimeter. N Engl J Med 1996; 335: 1081–90. 3. DELTA co-ordinating committee. DELTA: a randomised double- blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine or zidovudine alone in HIV infected individuals. Lancet 1996; 348: 283. 4. Lalezari J, et al. Improved survival and decreased disease progression of HIV in patients treated with saquinavir plus HIVID. XI International Conference on AIDS (Vancouver, July, 1996); LB.B.6033. 5. Katlama C on behalf of the CAESAR co-ordinating committee. Clinical and survival benefit of 3TC in combination with zidovudine- containing regimens in HIV-1 infection: interim results of the CAESAR study. 3rd International Congress on Drug Therapy in HIV Infection (Birmingham, UK, November, 1996): abstr SS2.1.) suggest that combination antiretroviral therapy was superior to nucleoside analogue monotherapy and that short-term changes in viral load (and also in CD4 count) predicted much of the treatment effect of these combinations. Smaller, short-term studies of triple-drug combinations or combinations of two protease inhibitors have revealed reductions in HIV plasma viral load by a factor of over 100, suggesting that these therapies may be clinically more beneficial than two nucleoside analogues in combination.

Some patients were so ill that clinicians at the time thought they would not survive. The use of these new drugs as part of a cocktail led to remarkable recovery and many of these patients are still alive today. In 1998, the British HIV treatment guidelines recommended the use of triple therapy; this was the start of the HAART (Highly Active Anti-Retroviral Treatment) era.

During these early 10 years we learned about drug resistance and how a combination of 3 drugs can prevent the emergence of HIV drug resistance. Advances in HIV virology and virological tests were essential to allow us to understand the dynamics of HIV replication. HIV viral load is a test that measures the amount of HIV virus was in the blood stream. This test which at one time was only available in research laboratories was shown to be an extremely useful test to determine the efficacy of the drug cocktail, very rapidly became available in the clinic in August 1996.

In 1997, British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals recommended that viral load measurement should be made widely available to physicians. We learned that if the patient's viral load was detectable while on treatment, HIV drug resistance is likely to emerge. This test also allowed clinician to explore adherence to HIV drugs. Over time, clinicians learned that if the HIV viral load was undetectable, the patient is taking his/her medication appropriately and that over time, their immune system would recover. Furthermore, if their viral load was undetectable, they were at a much smaller risk of developing new opportunistic infections. In 1998, clinical trials used a viral load assay with the lower limit of detection of less than 50 copies per ml and this new ultra- sensitive HIV viral load assay became available in the clinic in April 2003.

HIV resistance test started to become available in the clinic from 2000 onwards and allowed us to predict which HIV drugs that were be unlikely to be effective in our individual patients. In 2000, the British HIV treatment guidelines writing committee took the view that routine resistance testing should be recommended prior to therapy in chronically infected HIV patients, and that the clinician should be aware that treatment of naive patients may be complicated by pre-existing drug resistance.

HIV drug resistance is defined as reduced susceptibility to one or more drugs. There are two types of resistance test available; genotypic and phenotypic resistance assays. Phenotypic resistance is measured in the laboratory by

propagating the virus in the presence of a range of drug concentrations. This phenotype is determined by specific mutations within the HIV genome, which can be detected by genotypic analysis (nucleotide sequencing). Phenotypic resistance assay is a measure of the concentration of the drug required to inhibit either 50% or 90% of viral replication. This test is commercially available but expensive.

Genotypic resistance test is based on nucleic acid sequencing of the reverse transcriptase and/or protease genes of plasma viral RNA. Specific data on the relationship between genotypic mutations and reduced drug susceptibility have been generated through in-vitro experiments as well as clinical drug trials. Thus we identify mutations in the HIV reverse transcriptase and protease genes and infer reduced susceptibility to various HIV drugs.

HIV drug concentration

We became very quickly aware that patients were all different from each other in terms of the development of side effects, how the drug(s) were metabolised, how the drugs were absorbed or cleared from their body, and how the drug – drug interactions affected the drug level in the patient's body. Adverse drug-drug interaction would for example lead to a failure of the drug combination to suppress HIV infection. We learned that we had to measure the concentration of some drugs in the patient's blood stream and we learned of the importance of delivering adequate drugs in various parts of the human body; semen, via the placenta, brain etc.

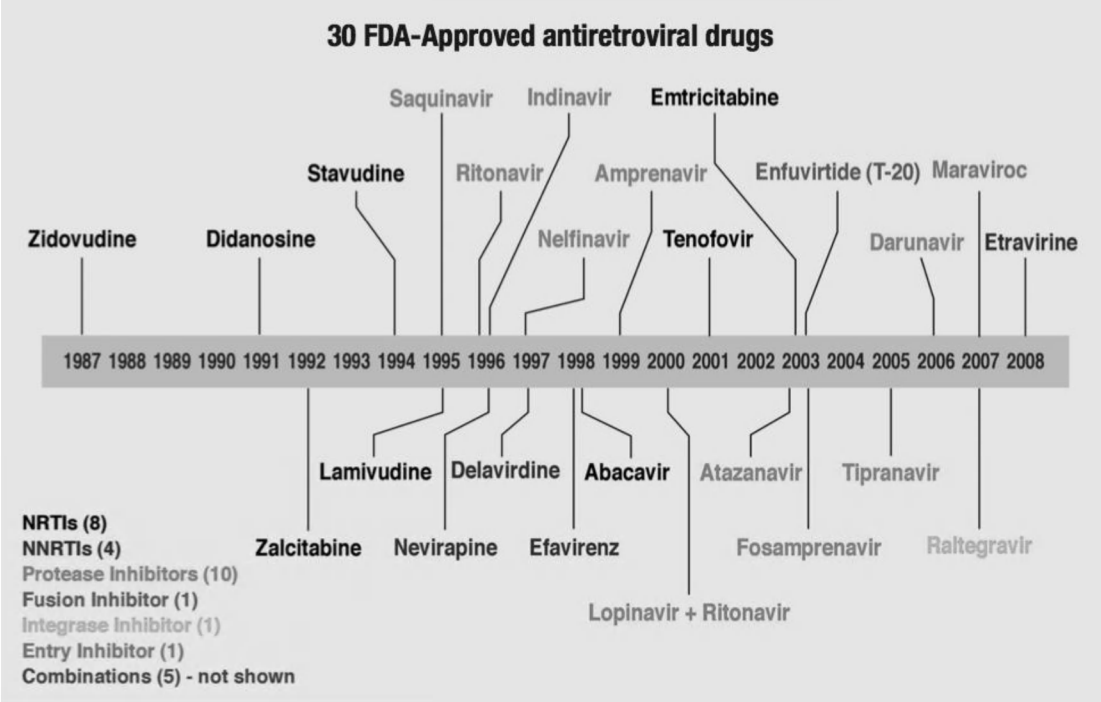
HIV can affect most organs of the body and in the early years of the epidemic, HIV associated dementia and other significant neurological complications were serious and disabling consequences of HIV. It was therefore important to ensure that HIV drugs could get into the brain in sufficient amounts as to suppress HIV replication in the brain. Similarly, the sexual transmission of HIV is thought to occur more readily if the amount of HIV is high in genital and rectal fluid; hence choosing drug(s) that can

achieve sufficient concentration in these fluids may reduce the risk of sexual transmission.

We now have around 30 individuals drugs from 6 drug classes that have been approved for use in the UK and there are a few more being tested. We are now very good at managing our patient, and now there are only a small number of patients who have run out or treatment options. The majority of patients have fully suppressed HIV infection while taking treatment; those who are not controlling their virus, have adherence issues. Despite a lot of effort to help these patients, we have great difficulty (and probably will not succeed) in maintaining long term HIV suppression.

Unfortunately, there is no cure as the virus starts replicating when the drugs are stopped. HIV can remain dormant in certain long lived latently infected memory cells in the body. Latent HIV is HIV that is not actively replicating. Instead, it lies dormant, often in immune system cells with long lifespans, such as memory cells (cells that "remember" bacteria and viruses from past infections so they can be effectively fought again). Since antiretroviral drugs usually work by blocking replication, they do not work on latent HIV.

As a result, antiretroviral drugs can never fully remove HIV from the body. Latent HIV will activate if therapy is stopped, renewing the HIV infection. There is some research to explore whether the HIV "reservoirs" can be treated to cure the patient.



Year individual HIV drugs approved by the US Food and Drug Administration

Nucleoside Reverse transcriptase inhibitors	Non-Nucleoside reverse transcriptase inhibitors	Protease inhibitors	Fusion inhibitors	Entry Inhibitors	Integrase Inhibitors
Zidovudine Didanosine Zalcitabine Stavudine Lamivudine Abacavir Tenofovir Entricitabine	Nevirapine Delavirdine Efavirenz Etravirine (Rilpivirine) Lesivirine	Saquinavir Ritonavir Indinavir Nelfinavir Amprenavir Lopinavir Fosamprenavir Atazanavir Tipranavir Darunavir	Enfuvirtide	Maraviroc	Raltegravir Elvitegravir

Co-formulations: Combivir, Kivexa, Truvada, Trizivir, Atripla,

The provision of such care and treatment to patients i.e. which hospitals/departments provide this

Prior to the mid 1990's, the care of patients infected with HIV was delivered by a variety of physicians including haemophilia doctors, respiratory physicians, gastroenterologist and genito-urinary doctors. From the mid 1990's onwards almost all inpatient care for HIV positive patients is delivered by infectious diseases doctors but the out-patient care is delivered by both ID physicians and GUM doctors. Very few general practitioners would treat HIV infection, although there is discussion to encourage General Practitioners to take on more of the care of HIV infected patients.

The efficacy of treatment for HIV and AIDS

In general without treatment around 50% of patients with AIDS survive 1 year but only 20% three years. Until the mid 1990's, treatment was not very effective. Patients could delay the progression of their disease by taking antiviral treatment using either one drug at a time or sometimes two drugs. Zidovudine was associated with improved prognosis but for no more than 2 years after starting therapy. The advent of a new class of HIV drugs (protease inhibitors) revolutionised the management of HIV infection. This was associated with the availability of HIV viral load measurement, the availability of HIV resistance tests, how to use resistance tests, how to encourage and monitor adherence to HIV treatment etc

Together with the increasing knowledge of HIV management, the availability of new drugs and new classes of HIV drugs, the prognosis of the HIV infected patient began to progressively improve over time. Newer drugs are not only more effective but they are also more simple and more tolerable to the patients. For example, co-formulation of drugs incorporating three drugs in a single tablet simplified the regimen and ease of administration.

A recent study of a multinational collaboration of HIV cohort studies showed that the projected life expectancy of HIV-infected treated individuals who were 20 years of age increased from 36.1 years in 1996 – 1999 to 49.4 years in 2003–2005. (The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008; 372:293 – 299). In another recent study from the Netherlands, the projected median number of years lived from age 25 was 52.7 (IQR 44.2–59.3; general population 53.1) for men and 57.8 (49.2–63.7; 58.1) for women without HIV related symptoms (CDC-B event). The number of life years lost varied between 0.4 if diagnosed with HIV at age 25 and 1.4 if diagnosed at age 55; for patients with HIV related symptoms (CDC- B event) this range was 1.8–8.0 years (A van Sighem et al. AIDS 2010, 24:1527–1535)

Currently, most HIV physicians believe that with treatment most HIV infected patients will have a near normal lifespan. With near perfect adherence to HIV treatment, the virus is fully suppressed in the blood stream, and over time with full suppression, the immune system recovers and may eventually return to normal. Unfortunately, there is no cure and if treatment is stopped, the immune system gradually deteriorates and the patient becomes symptomatic.

When HIV is fully suppressed by treatment, it is believed that the infectiousness of the patient is decreased significantly. So the risk of transmission through sex or through blood contamination is low. Even transmission from mother to child at delivery is dramatically reduced. If the mother's HIV is fully suppressed with HIV treatment, the risk of transmitting HIV to her child at delivery is very low. Spontaneous vaginal delivery is now an accepted clinical practice for mothers whose HIV viral load is undetectable; a major change from early clinical guidelines that used to only recommend Caesarian Section to prevent mother to child transmission.

UK Experts are currently reviewing whether HIV infected health care workers performing exposure prone procedures (for example surgeons and dentists)

can be allowed to work normally if their HIV infection is fully suppressed on HIV treatment. This group of healthcare workers are currently not allowed to perform exposure prone procedures under current guidelines.

These reflect the tremendous progress that has been achieved in the field of HIV management.

The side effects of such treatment

Earlier drugs were associated with many side effects affecting many organs. Side effects of earlier drugs include: headache, nausea, vomiting, diarrhoea, flatulence, skin rashes, liver inflammation, kidney stones, dysphoria, weird and sometime frightening dreams, depressive symptoms, tiredness, poor sleep, and body shape changes. Diarrhoea is particularly troublesome and is usually associated with protease inhibitors. Additional medication was prescribed to mitigate the side effects and hence increased the pill burden to the patient. Sometimes, if the side-effects were significant, the patients would miss the pills or the physician would need to change the treatment regimen. In certain situations, there were no alternative drug and it was up to the patient to decide between putting up with the side effects or to stop the medication. Taking less than the prescribed dose was not advised at it might lead to increasing HIV resistance. Fortunately, this is now a rare occurrence.

Body shape changes are very distressing for most patients. There are two different types of body shape changes that are seen. One is fat loss usually around the face and on the arms and legs. Patients' veins become prominent as a result of the fat loss in arms legs and buttocks. The facial fat loss is more distressing as the patient appears to have lost weight and look like cachectic AIDS patients with late stage HIV disease. Fat loss is thought to be associated with the use of Thymidine analogues; these include zidovudine and stavudine. Body shape changes can be stigmatising and distressing, often resulting in low self-esteem, isolation and depression. This has led to many patients asking to stop their HIV medication.

The other body shape change is fat accumulation around the belly and back of the neck. This can co-exist with the fat loss and the combination makes the patient's appearance quite abnormal. There is now some surgical reconstruction available to partially reverse some of these changes. Fat accumulation is thought to be associated with the use of protease inhibitors in particular drugs like indinavir, ritonavir. It is though that this is less likely to be associated with the newer protease inhibitors like lopinavir, darunavir or atazanavir.

Morbidity among patients with HIV infection on treatment

HIV treatment is associated with an increased risk of cardiovascular disease; this is particularly the case among patients taking protease inhibitors. Metabolic changes are also seen in patients taking anti-retroviral treatment; these include diabetes mellitus, raised levels of lactic acid, raised cholesterol and triglycerides. HIV therapy is also associated with raised levels of liver enzymes. There is also an increased risk of fractures among HIV positive patients. It is unclear whether the changes we are seeing today represent toxicity of the antiretroviral treatment or an accelerated ageing process in the HIV infected population. Research is ongoing in this area.

This has to be placed in the context that the treatment has transformed a potentially fatal condition into a chronic condition with long-term morbidity. The risk of cardiovascular disease without HIV treatment is much higher than with HIV treatment. The side effects of the HIV medication can be managed by changing HIV drugs, and by the use of other medication to mitigate the impact of the side effects. Patients with HIV are monitored carefully, but as the HIV infected population age, we are likely to observe the interaction of ageing and HIV infection.

The effect on such treatment, if any, of a patient having haemophilia.

The only significant effect of HIV drugs in a patient with haemophilia is that the early drugs in the protease inhibitor class was associated with an increased tendency for increased bleeding times and hence for the need for more clotting factor replacement. As the number of HIV infected haemophiliacs declined, experience with any new HIV drugs became increasingly limited. This may explain why very few reports of toxicities peculiar to haemophiliacs have been published in the medical literature.

Effect of HCV on HIV infection

HCV may have a deleterious effect on HIV progression. Some studies have demonstrated that HCV infection was independently associated with an increased risk of progression to AIDS or death, despite a similar use of antiretroviral therapies in the coinfected group compared with the group infected with HIV alone. A Swiss study also suggested that those patients with dual infection may be less likely to achieve a CD4 count rise of at least 50 cells/mL within 1 year of starting HAART than those with monoinfection. The HIV viral load response to therapy was similar, however, in patients with and without HCV. This deleterious effect is confirmed in some, but not all other studies

The effect of HIV on HCV infection

Only 20–30% of immunocompetent individuals with HCV will progress to cirrhosis over an average of 15–30 years. Evidence suggests that in HIV-positive individuals progression is likely to occur more frequently and at a faster rate. One study estimated the median time to cirrhosis as 32 years and 23 years from time of acquisition in HCV-infected and HCV/HIV-coinfected individuals, respectively. This is now manifest as a proportional increase in deaths from end-stage liver disease throughout the HIV-infected population such that HCV infection is one of the major causes of death in people with HIV.

Coinfected patients have comparably higher levels of HCV in the blood stream and in other body fluids and these are inversely correlated with the CD4 cell count and degree of immunosuppression present.

Several studies show that liver-related mortality rates are higher in those with a low CD4 cell count, irrespective of ART use. There is some evidence that demonstrate a better outcome for the coinfected patients with suppressed HIV infection compared to those with poorer HIV control. Guidelines have also suggested starting HIV treatment for those coinfected with HCV at an earlier CD4 cell count compared to those mono-infected with HIV.

Hepato-cellular carcinoma is estimated to occur at a rate of 1–4% per annum in patients with HCV-related cirrhosis; in patients who also have HIV infection it tends to occur at a younger age and within a shorter time period.

The response to HCV treatment with current standard of care (Pegylated Interferon plus ribavirin) is impaired in the HIV coinfected patient compared to the HCV monoinfected patient. This has led to many coinfected patients deferring HCV treatment until better treatment options become available.

The effect on such treatment, if any, of a patient being co-infected with the Hepatitis C virus

All antiretrovirals have the potential to cause acute and long-term hepatotoxicity and this risk is increased two- to threefold in the presence of chronic liver disease such as that caused by hepatitis B or C.

Current literature suggests that those patients with fully suppressed HIV tend to have a slower rate of progression of their liver disease. As a result, the British HIV Association HIV treatment guidelines (2008) state that treatment may be started or considered before the CD4 cell count falls below 350 cells/μl in patients with hepatitis C infection, where treatment for hepatitis is deferred.

The difficulties, if any, for patients taking such treatment

Anti retroviral treatment can be difficult in the sense that for it to be effective, treatment will need to be taken as directed. When zidovudine was first used in 1987, it was recommended that the patient took the medication at 4 hourly intervals. Zidovudine was associated with nausea, headaches and anaemia. Taking the drug at 4 hourly intervals meant that patients used to use timers to wake them up during the night so that they were reminded to take their treatment. Consequently, many patients complained of tiredness and anxious about their treatment adherence,

Although some treatments are taken twice a day, the interval between doses should be around 12 hours plus or minus 1 hour. Some treatments are best taken with food and others on an empty stomach in order to maximise drug absorption. Sometimes, the anti HIV regimen may contain some drugs that need to be taken on an empty stomach and others that need to be taken with food. This is very cumbersome and is a barrier to good adherence.

Frequent complaints around the mid 1990's included the number of tablets to swallow, the large size of the tablets or capsules, the difficulty in swallowing the tablets because of their shape. These physical problems were often overshadowed by the side-effects of the treatment as outlined earlier. One drug (enfuvirtide) had to be administered by subcutaneous injection twice daily. It took a long time to reconstitute and in the early years had to be stored in a fridge. These are obstacles to adherence.

The side-effects may put some patients off particularly if their mood is low and if they are not feeling well after taking the medication. Taking the medication reminds patients that they have HIV infection and this also puts them off taking treatment. Remembering to take treatment every day of their lives and not just for one week is very difficult and sometimes patients have treatment fatigue. Some patients are frightened about missing their

medication because of the risk of HIV drug resistance. Taking HIV treatment can therefore be very stressful and can cause a lot of anxiety.

Non-disclosure of HIV status impairs the patient's ability to adhere to their HIV treatment. Until recently, some drugs e.g ritonavir and enfuvirtide had to be stored in a fridge and patients who had not disclosed their HIV status could not use these drugs for fear of disclosure. Similarly, these patients would conceal the fact that they are on some form of medication and this also hindered their ability to take the medications as directed by the doctor.

Some medication may affect sleep and may cause light-headedness/unsteadiness and this would be unsuitable if they did shift work or had to drive; this limited the treatment options available to them.

If the patient experiences physical side effects, then the treatment becomes even more difficult. Physicians prescribe additional medication to counteract the side-effects, adding to the pill burden; these include anti-sickness medication, antidiarrhoeal agents like Imodium and painkillers for headaches.

The effect of non-adherence to prescribed treatment for HIV and AIDS

Non-adherence to prescribed treatment for HIV leads to the emergence of drug resistance and subsequent failure of the anti HIV regimen and immunological deterioration. Patients became ill again. HIV drug resistance also means that other drugs in the same class may be less effective and resistance limits future options for the patient. Within drug class resistance also means that new classes of drugs are required to ensure the success of anti-HIV therapy.

Effect on the families of patients infected with HIV

HIV has a huge physical and psycho-social impact on HIV infected individuals and their families. The stress of living with HIV causes some people to suffer from mental health problems such as anxiety and depression.

As with other chronic illnesses, partners and families often provide most of the physical and emotional care. They can provide support with treatment, adherence to treatment. This can place a great strain on them. This can lead to individual stress and tension between members of the family. In relationships, the diagnosis of HIV may reveal aspects of a person's behavior that they may have wanted to keep private. This may include infidelity or sexuality (such as male homosexuality) or intravenous drug use. This can result in feelings of guilt, blame and lead to a relationship breakdown.

The family may also have to face bereavement. This was certain the case prior to 1996. Now families are learning to deal with HIV as a chronic disease affecting the lifetime of the infected members.

With HIV, more than one person in a family may be unwell which can add to the burden of care and cause additional emotional and financial problems.

Stigma and discrimination may lead to the diagnosis being kept hidden. This can prevent wider support from extended family or the community. Prior to disclosing their status to their children, parents may first have to deal with the anger, fear, depression related to their own HIV diagnosis. Often, this disclosure never happens even when their children are grown up and have left the parental home.

A family with an infected child will have to consider when and how to disclose this to them.