

aids treatment update

non-hodgkin lymphoma

As this month's issue was being put together, the 2001 revision of the British HIV Association's Antiretroviral Treatment Guidelines were made public on aidsmap.com in their final form for the first time. This document, which advises doctors and patients on how best to use, monitor, and support anti-HIV therapy, according to current knowledge, is one of the most influential documents of its kind anywhere in the world.

This year's guidelines contain a number of recommendations which are likely to court controversy, (and ATU will be pouring over these in more detail next month). Amongst these is the move towards beginning anti-HIV treatment at lower CD4 levels than before. Though the immediate pressures for this change are concrete rather than theoretical – unexplained side-effects being one example – what will result over the longer-term can only be guessed at. Over the page we consider how the use of HAART in the recent past has altered the pattern of HIV-related disease we see today, and the further change we might expect in future.

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non-hodgkin lymphoma

2 has use of HAART made Non-Hodgkin lymphoma less common, and should HAART be used to treat it? by anna poppa

Since the introduction of triple combination therapy (HAART) in many prosperous countries during the late 1990s, the rate at which people with HIV have developed AIDS, or died as a result, has fallen dramatically. Though most AIDS-defining illnesses now have a much reduced incidence in countries such as the UK, Non-Hodgkin lymphoma (NHL), a type of cancer which is diagnostic of AIDS, has not appeared to wane to the same extent. In fact it's been unclear whether the incidence of NHL has been affected by the HAART era at all.

What is NHL?

NHL is a type of lymphoma; a tumour that occurs as a result of uncontrolled multiplication of white blood cells called lymphocytes. NHL may occur either in the lymph nodes or elsewhere, such as the spinal cord and brain (in which case it is termed primary CNS lymphoma), the gastrointestinal tract, the liver or kidneys. More unusually, NHL may affect sites such as the anus, rectum, mouth, muscles or other soft tissues. If the lymphoma occurs outside the central nervous system, it is called systemic lymphoma. NHL is also known as Burkitt's lymphoma, and as B-cell lymphoma, after the type of lymphocyte whose proliferation NHL involves. (The other main type of lymphoma is Hodgkin's disease).

In the general population, NHL predominantly affects the elderly, but it is also the most common lymphoma seen in people with HIV. NHL among people with HIV is more aggressive, and responds less well to anti-cancer therapy (known as chemotherapy), than in HIV-negative people. Though NHL can occur at a wide range of CD4 counts, it is more

common in people with CD4 counts between 100 and 200 cells. Unlike Kaposi's sarcoma (KS), another AIDS-defining cancer which predominantly affects gay men, NHL is seen in all communities affected by HIV.

The prognosis of those who develop NHL has historically been poor, but recent reports suggest that the advent of HAART seems to have extended survival, and this is discussed in more detail below. In the past, people with AIDS-related NHL lived for an average of four to eleven months after their NHL diagnosis, depending on the severity of immune suppression, while those with primary CNS lymphoma lived for an average of two to four months, regardless of CD4 count.

The cause of the B-cell proliferation seen in NHL is unknown. Possible causes include:

- HIV-related disruption to normal levels of inflammatory cytokines (chemical messengers) such as IL-6 and IL-10, which in turn stimulate B-cells.
- Repeated stimulation of B-cells by organisms such as viruses. Whilst HIV is clearly a common factor in AIDS, another candidate is Epstein-Barr virus (EBV), which can be isolated from many people with NHL. EBV is, however, a common virus which infects most people by adult life. On infection it may cause glandular fever, but afterwards it stays dormant in cells.
- HIV-related damage to the germinal centres of the lymph nodes. This is where B-cells are normally exposed to foreign organisms.

NHL in the age of HAART

Historically, NHL was seen relatively infrequently amongst people with AIDS. Of 97,000 AIDS cases reported to the US disease surveillance centre in Atlanta prior to 1989, fewer than 3% had NHL. Today, however, NHL is a more frequent diagnosis amongst people who become ill with AIDS-related disease, and who die, despite the availability of HAART. Data from the French Aquitaine cohort were presented at this year's Retroviruses Conference in Chicago. NHL accounted for 28% of AIDS deaths between 1998-1999.

Because lymphoma is in part the result of both immune deficiency, and long-term over-stimulation of the immune system, it may have been expected that the introduction of HAART would raise the incidence of NHL. That's because one effect of HAART has been to keep many people alive with compromised immune systems for longer than would have been the case before HAART was in use. Though HAART's effect on reducing incidence of other opportunistic infections (such as PCP, MAI, CMV) was apparent some time ago, it's possible that longer periods may be required to see an impact on NHL. Epidemiological information appears to support this idea.

Early data from the US were reported by Susan Buchbinder in the *Journal of AIDS* in 1999. Her group found that of 6,704 gay men in the San Francisco City Clinic cohort, there was no significant reduction in the annual rate of NHL after the introduction of protease inhibitors (PIs), (2.2 cases per 100 patient-years in 1993 to 1995, versus 1.8 cases per 100 patient-years in 1996).

In the same year, Ledergerber reported data from the Swiss HIV Cohort Study in the *British Medical Journal*. These data reflected the experiences of 6,636 people with HIV followed over 18,498 person-years, comparing new AIDS-defining conditions between 1992 to 1994 (pre-HAART), and between 1997 to 1998 (post-HAART). Overall, new AIDS-defining illnesses fell from about 150 per 1,000 person-years to 35 per 1,000 person-years. However, the number of new cases of NHL did not decline.

Late in 2000 in *Blood*, Mark Bower and colleagues reported data from the Chelsea and Westminster Hospital, London. Dr Bower studied AIDS-related lymphoma among a cohort of 7,840 HIV-positive gay and bisexual men. Between 1988 and 1995 there were 95 cases of lymphoma, and 51 cases between 1996 and 1999. Between these two periods, which reflect the pre- and post-HAART era, the annual incidence of lymphoma did not change, but did contribute to a greater proportion of first AIDS-defining illnesses.

Researchers from Australia described incidence of NHL in people with HIV in the journal *AIDS* earlier this year. Follow-up of 8,108 people found a lower incidence of NHL in the period following the introduction of HAART compared to that before. NHL incidence had decreased less than KS had decreased, however.

Data from the EuroSIDA cohort of Europeans with HIV, presented at the International AIDS Society conference in July, similarly buck the earlier trend. 8,471 people were followed between 1994 and 2000, providing 26,764 person-years of follow-up. During this period there were 222 cases of NHL. When the period before September 1995 (pre-combination therapy) was compared with the period which followed that cut-off (post-combination therapy), the incidence of NHL fell from 1.99 cases per 100 person-years to 0.30 cases per 100 person-years. In people who started HAART, incidence was lower after 24 months of therapy than in the first 12 months. In addition, those who did develop NHL tended not to have sustained a good response to HAART.

Nevertheless, some experts warn that it may still be too early to draw firm conclusions about the likely incidence of NHL in the future – particularly in the light of the recent move towards delaying anti-HIV treatment until the CD4 count has fallen nearer the 200 cell mark. They argue that NHL should be expected to be seen more frequently in people who endure long periods of immune suppression. Citing the experience of other patient groups, Dr Barry Peters, of St Thomas' Hospital, London, told *ATU* "In renal transplant patients there is evidence that the duration of immune

glossary

antiretroviral A substance that acts against retroviruses such as HIV.

baseline Starting point or value.

CD4 A molecule on the surface of some cells onto which HIV can bind. The CD4 cell count roughly reflects the state of the immune system.

CMV Cytomegalovirus, a virus that can cause blindness in people with advanced HIV disease.

granulocytes Immune cells in the blood which can attack bacteria and fungal infection. Also called neutrophils.

HAART Highly Active Antiretroviral Therapy, a term used to describe anti-HIV combination therapy with three or more drugs.

lymph nodes Areas in the body where white blood cells and other important immune cells are found. Also known as glands.

MAI Mycobacterium avium intracellulare, a micro-organism related to TB which can cause disease in people with advanced HIV.

NNRTI Non nucleoside reverse transcriptase inhibitors, a family of antiretrovirals that includes efavirenz and nevirapine.

NRTI Nucleoside reverse transcriptase inhibitors, a family of antiretrovirals that includes AZT, ddI, d4T and 3TC.

opportunistic infections Specific infections which cause disease in someone with a damaged immune system.

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suppression is influential [to their risk of NHL], so we shouldn't be too quick to assume that the incidence of NHL will fall in people with HIV – it may increase."

How should NHL be treated?

The best way to manage HIV-positive people with NHL in the age of HAART has not been clear. The standard treatment for NHL involves chemotherapy with combinations of anti-cancer drugs, (though primary CNS lymphoma may be treated locally using radiotherapy). No one combination has been well-established as superior, and though the availability of HAART appears to have increased survival following NHL diagnosis, there are significant challenges in combining the use of anti-HIV and anti-cancer therapies.

Chemotherapy tends to be associated with extreme side-effects, which may be worsened by the use of additional medication. Drug interactions can also reduce effectiveness by altering the metabolism of the chemotherapy, and this can have a significant effect on the outcome. Chemotherapy is given in cycles; usually once every two months for six months. Medication for nausea and anxiety are usually given at the same time. Another treatment, G-CSF (granulocyte colony stimulating factor), may also be given to stem the loss of certain white blood cells. Because chemotherapy is immunosuppressive, treatment to prevent opportunistic infections such as PCP is likely to be needed too. All in all, this is a lot of medication for individuals to tolerate, and to adhere to, and presents significant scope for problematic drug interactions.

For these reasons there has been some debate over whether HAART is best suspended or delayed whilst cycles of chemotherapy for NHL are administered. Some doctors argue that NHL presents a greater threat to survival than HIV and so should be treated preferentially. One advocate of this approach, Richard Little of the US National Cancer Institute, has reported positive data on the administration of

a dose-adjusted chemotherapy regimen (EPOCH) to 23 people with NHL who suspended their antiretroviral therapy. Six months post-treatment, CD4 counts had recovered to near or above baseline in all but two people, and after two years, sixteen people had complete remission of NHL.

However, in August in the journal *AIDS*, an Italian group reported on the use of chemotherapy with concomitant (given at the same time) HAART in 44 people with NHL. They found that remission was more likely to occur in those who had a good response to HAART (71% versus 30%), and that virological response to HAART was the only factor associated with tumour response in multivariate analysis. Patients with a virological response to HAART were more able to tolerate a higher dose of chemotherapy, and had an increased survival rate one year following diagnosis of NHL.

At an AIDS and malignancy meeting in Bethesda, Maryland, earlier this year, similar findings were reported in relation to treatment of primary CNS lymphoma. Cinque reported on use of HAART in people with primary CNS lymphoma by retrospective review of 66 people diagnosed after 1993. Twenty-three people received HAART, fourteen of whom started or continued after their lymphoma diagnosis. After one year, 26% of those who had taken HAART were still alive compared with 2% of untreated patients. However, the survival rate was greater (43%) in those who received HAART after diagnosis. The most profound difference in survival was seen when those who started HAART after their NHL diagnosis were compared with those who started before (71% versus 0%). After controlling for the effect of chemotherapy, only starting HAART after diagnosis was associated with decreased risk of death, suggesting that effective HAART was crucial to outcome.

At the Durban International AIDS Conference

last year there were two further reports concerning concurrent treatment strategies. Romeu reported on response to one of the older chemotherapy combinations (known as CHOP) in 58 individuals with lymphoma who were treated between 1988 and 1999 in Badalona, Spain¹¹. Treatment with both CHOP and HAART was associated with a six-fold greater likelihood of complete remission (75% versus 34%).

Corales reported full resolution of primary CNS lymphoma in two people treated with HAART alone¹². One had an initial response within three months of beginning treatment, with full resolution after 21 months.

Managing drug interactions

Practice at the Chelsea and Westminster Hospital is to offer concurrent chemotherapy and HAART, using NNRTIs where possible as these present fewer drug interaction problems than other antiretroviral classes. Clearly, antiretroviral treatment options will be based on an individual's prior treatment experience.

Limited information is available on the HIV Drugs Interactions website run by the Liverpool HIV Pharmacology Group (<http://www.hiv-druginteractions.org>). They provide information on potential interactions between PIs and NNRTIs and five anti-cancer drugs:

cyclophosphamide (*Endoxana*), doxorubicin (*Adriamycin*), paclitaxel (*Taxol*, used to treat KS), vinblastine (*Velbe*), and vincristine (*Oncovin*). This advises that doxorubicin does not interact with anti-HIV drugs (whereas the other agents do), and that nevirapine presents fewer problems than other antiretrovirals.

Drugs from the NRTI class do not present the same type of drug interaction issues associated with PIs and NNRTIs as they use different routes to pass through the body. However, their use in combination with chemotherapy may still be problematic because of overlapping side-effect profiles. AZT plus chemotherapy increases the risk of bone marrow suppression and so is generally not used in this setting. 3TC, d4T and ddI present fewer problems. There appears to be little information on the use of abacavir with chemotherapy. It may be a concern that symptoms of the hypersensitivity reaction associated with this drug may be difficult to distinguish from the systemic side-effects seen during chemotherapy.

Given that the daily pill burden may be quite high, taking liquid formulations of anti-HIV medications may be preferable for some people. In addition, chemotherapy can cause mucositis, an inflammation of the mucous membranes which may cause difficulty with swallowing.

key conclusions

- Since the introduction of triple combination therapy for HIV, known as HAART, most opportunistic illnesses seen in people with HIV have become much less common in those countries where these drugs have been available.
- It has not been clear whether the incidence of Non-Hodgkin lymphoma has also been reduced by HAART, but new information suggests this is the case.
- The usual treatment for NHL is cancer chemotherapy. Evidence suggests that this is most effective where people also take anti-HIV treatment at the same time. This can present problems with drug interactions and side-effects, however.
- Close communication between patient and doctor, and between the HIV physician and the cancer physician ensures that respective areas of expertise are shared.

glossary continued

PCP Pneumocystis carinii pneumonia, a form of pneumonia.

protease inhibitors Family of antiretrovirals that includes indinavir, saquinavir, ritonavir, nelfinavir.

radiotherapy Treatment using radium or other radioactive matter.

further reading

References, and a more detailed review of this subject, are available online at NAM's website, aidsmap.com

learning from clinic databases

6 what are the risks in using clinical databases to draw conclusions about the effects of antiretroviral treatment? by caroline sabin

In health care settings the efficacy of any new treatment is usually assessed in a randomised controlled trial (RCT). Information from RCTs is perceived to be the most robust form of evidence available and is rated highly when assessing the value of new treatments (see, for example, the 2000 BHIVA treatment guidelines¹). However, in the HIV field it has become increasingly difficult to carry out RCTs of new antiretroviral combinations since the introduction of HAART, and those that are carried out may be limited in scope.

In an RCT it is usual to compare only one, or occasionally two, new treatment combinations to a standard regimen (which is usually stated to be 'standard of care'). Thus, of the many hundreds of possible treatment combinations available, only two or three combinations are compared in any trial. Furthermore, definitions of what is standard of care may vary greatly and a combination which is standard of care at

the start of a trial, may not be by the time the trial has been completed.

Because of the dramatic reduction in opportunistic infections and death since the introduction of HAART most trials now use surrogate marker endpoints based on changes in the viral load level. This means that there is little information from RCTs on the clinical benefits of different treatment combinations.

As there is a desire to complete trials as quickly as possible, trials are often of limited duration and thus there is rarely any long-term follow-up of trial participants. Therefore, these trials address questions which relate to the initial treatment combination but do not address long-term strategic issues.

Individuals recruited to RCTs are often not typical of the clinic population, usually because the trial itself restricts entry, or because those

who choose to enter trials may differ from those who choose not to enter trials². Therefore, it may not always be possible to generalise the results from RCTs to the whole clinic population.

Trial follow-up is often more frequent and regular than that in a routine setting, again limiting the applicability of results from trials.

For these reasons, concerns have been raised that the RCTs currently underway may not address the issues of primary interest to many patients or doctors. Therefore there has been some interest in whether clinic databases can be used to address some of these issues.

What is a clinic database?

When an individual attends an HIV treatment centre for HIV care, information is routinely collected on that individual. This may include demographic information (eg. age, sex and ethnicity), treatment history and any CD4 counts and viral loads. This information allows decisions about an individual's care to be made quickly and accurately. However, there are a number of other ways in which this information may be used to improve general patient care. Firstly, at a clinic level, centres may use this information to see how their clinic demographics are changing and to predict their future resource requirements. Secondly, such information has been invaluable in defining the importance of the CD4 count and viral load as markers of disease progression. Finally, limited information is provided to the Communicable Disease Surveillance Unit, who monitor the HIV epidemic in England and Wales.

Because of the limitations of RCTs it has been suggested that this information could also be used to assess the relative benefits of different treatment combinations. Information on virological, immunological and clinical responses in individuals receiving different antiretroviral combinations can be compared in order to identify combinations which are associated with a less favourable outcome, ultimately meaning that individuals will receive more effective therapies.

The benefits of using clinic data over an RCT are primarily to do with the ease and speed of

data collection. However, there are other benefits which make this approach appealing. As data is collected on *all* individuals registered at a centre and, by definition, the frequency of follow-up is the same as in the clinic, the results are directly generalisable to that clinic. Furthermore, as long as sufficient numbers of individuals are receiving each treatment combination, then any number of treatment combinations can be compared (in practice, however, the number of possible treatment combinations is still limited by the number of individuals receiving treatment in the clinic).

Clinic databases do, however, have limitations which must be considered. One of these relates to the scrutiny with which information is gathered; the information a database can generate is only as good as that put in. If individuals differ with regard to the diligence with which they input data, this could become a source of bias.

Making treatment comparisons

Consider the situation where we are interested in the clinical outcomes of antiretroviral-naïve individuals starting one of two different HAART combinations, A or B. In order to perform the analysis, information is extracted from the clinic database on all antiretroviral-naïve individuals at the clinic who started HAART with one of these two combinations. The clinical event rate (the number of clinical events occurring divided by the total follow-up time) is calculated in the two groups and these are compared. This provides an estimate of the *treatment effect* – a measure of how much better (or worse) combination A is compared to combination B. This will be an unbiased comparison of the two combinations, *provided* the two groups do not differ systematically at the time of starting treatment in any respect other than the treatments received.

Unfortunately, this is where the major limitation of clinic databases becomes apparent. In an RCT, the equivalence between the two groups is achieved through randomisation and any differences in clinical outcome at the end of the trial can therefore be attributed to the treatments received.

editor's note

This article provides further discussion of the different methods researchers are using to learn about the effects of HIV treatments, and the best ways of using them. Last month, Caroline reviewed the pros and cons of the range of approaches taken when analysing information from trials.

glossary

See also pages 3 and 5.

adherence The act of taking a treatment exactly as prescribed.

clinical event The occurrence of a physical sign or symptom, rather than an abnormality that can only be detected by laboratory tests.

clinical trial A research study with people, usually to find out how well a new drug or treatment works and how safe it is.

endpoint An event used by a clinical trial to evaluate whether a trial therapy is working, e.g. developing AIDS or a rise in viral load above a certain level.

naïve Never having taken anti-HIV drugs before.

randomisation The process of selecting by chance the treatment that a clinical trial participant will receive.

regimen A drug or treatment combination and the way it is taken.

surrogate marker An indirect indicator of something, such as measuring viral load to assess the treatment effect of a drug.

toxicity The extent or ways in which a drug is poisonous to the body.



learning from clinic databases continued

However, in a clinic setting, the choice of which treatment an individual receives is made by the individual and his/her doctor after careful discussion of a number of factors, including the individual's stage of disease, their lifestyle, previous treatment history and the treatments currently available. Thus, there is no guarantee that patients receiving combinations A and B will be similar; in fact, the patients in the two groups are likely to be very different.

These treatment comparisons are further complicated by the fact that different treatments have been introduced into clinical practice at different times. If, say, the drugs in combination A have been available since 1997 whereas those in combination B have only been available since 2000, then individuals starting combination A may have started treatment anytime between 1997 and 2000, whereas those starting combination B may only have started it from 2000 onwards. Many other factors also change over time, including the support provided to help maintain good adherence and the medications available for alleviating some of the drug toxicities. Furthermore, as treatment guidelines have changed, the CD4 count and viral load at which individuals usually start treatment has changed. All of these factors are likely to have an impact on an individual's expected response to therapy. Factors which are associated with treatment outcome and which may differ between the treatment groups in this way are known as *confounding factors*.

The usual way to deal with these confounding factors in order to reduce bias is to *adjust* for them in a statistical model. For example, if those starting combination A tend to have higher viral loads than those starting combination B, then we adjust for viral load in the analysis.

Although adjusting for confounding factors is generally successful, it does have two main limitations. Firstly, we can only adjust for

factors which are known about and which are recorded on the database. Thus, it is not possible to adjust for unknown confounding factors which may systematically differ between the two treatment groups. In an RCT even the unknown factors will be randomly distributed across the treatment arms, but in a clinic database this may not be the case. Secondly, if the individuals in each treatment arm completely differ on one factor (for example, if *a*// patients receiving combination A started treatment in 1997 and *a*// patients starting combination B started treatment in 2000), then we cannot adjust for this factor – there has to be some 'overlap' between the individuals in the two groups so that an adjustment can be applied.

In either case, the adjustment for confounding factors will not be completely successful and some residual bias may remain which may affect the validity of the treatment comparison. The question of importance is whether, after adjusting for all of the known confounding factors, this residual bias is large enough to lead to seriously misleading conclusions about the value of the new treatment. Unfortunately, studies which have considered this issue³ have reported that although similar results are generally obtained from RCTs and observational databases, in some cases it is possible to get very misleading results.

The use of different viral load tests

There is a second area which creates problems when analysing data from clinic databases, particularly when considering virological responses to therapy, and this relates to the fact that the tests used to quantify viral load have changed over time.

Tests used to detect viral load have become more sensitive over time. Thus, although the viral loads themselves may not have actually changed, the value recorded on the database will change (values previously recorded as below 400 copies may now be recorded as lower values) leading to an apparent decline in viral load over time.

These tests are now less likely to be affected by the infecting subtype of HIV. Centres with a

high proportion of individuals infected with non-B subtypes, (the type of HIV found outside the US and Western Europe), may see an apparent increase in the viral loads of their clinic population, simply because some of the early measurements were falsely low.

There is variability between the different tests and some tests tend to give consistently higher viral load measurements than others. If the test used is changed over time, then this can lead to a systematic change in the viral load levels recorded on the database.

The frequency of viral load monitoring may have changed over time. If viral loads are measured monthly then an individual will probably have a viral load measured below 50 copies sooner than s/he would have done if viral loads were measured less often.

In a clinical trial, the same type of test is generally used for the whole duration of the trial, and the frequency of monitoring is constant. Therefore these issues do not usually affect any treatment comparisons made. However, in a clinic setting, where the choice of test and rate of monitoring is dictated by laboratory protocols and treatment guidelines, any changes in the choice of test can have implications for the interpretation of clinic data. Methods are available for adjusting for the use of different tests, but they may not be completely reliable.

What does this all mean?

RCTs remain the gold standard method of assessing new treatments in HIV infection.

However, some of the limitations of RCTs means that clinic databases are increasingly being used to draw conclusions about the value of new treatments and treatment combinations. This is not in itself a bad thing as it is important to obtain as much information from these databases as possible. However, because of the possible limitations with clinic databases it is important to ask a number of questions of the analysis when interpreting the results from these studies:

- Have all known confounding factors been adjusted for in the analysis or are they similar in the groups at the time of starting treatment? In particular, have the authors adjusted for disease stage at the time of starting therapy, treatment history and calendar year (to control for other changes in medication and adherence support)? Is it likely that the treatment groups compared may systematically differ on any other factors which have not been measured?
- It is always more believable if two or more independent studies have reported similar findings. Therefore, is this study the first to show such an effect or has it confirmed other findings?
- Is the treatment effect large or small? If there are only small differences between the combinations being compared then it is possible that this may be due to some residual bias. If, however, the difference between the two treatments is very large, then it is unlikely that all of the effect can be explained by residual confounding.

key conclusions

- Whilst randomised controlled trials (RCTs) are the gold standard approach to assessing the value of new treatment combinations in HIV infection, some key questions remain unanswered by RCTs.
- A large amount of information is collected on individuals at each clinic visit. There is a

suggestion that this information could be used to draw conclusions about the relative benefits of different treatments.

- Whilst the use of clinic databases is appealing, they have several limitations and there is the potential for bias in any treatment comparison.

references

- 1 BHIVA Writing Committee. HIV Medicine 2000; 1: 76-101.
- 2 Madge S et al. HIV Medicine 2000; 2: 212-218.
- 3 Phillips AN et al. AIDS 1999; 13: 2075-2082.



Hepatitis G may slow HIV disease

An apparently harmless hepatitis virus appears to slow HIV disease progression, according to recent reports in the *New England Journal of Medicine*. Hepatitis G virus, also known as GB virus, is found in about 2% of healthy blood donors in the USA and up to 35% of HIV-positive individuals. It has not been associated with any form of liver disease or other pathology.

University of Iowa researchers found that around 40% of HIV-infected individuals in their cohort were infected with GB virus. When they compared disease progression rates of people with and without GB virus infection in 362 HIV-positive individuals who received anti-HIV treatment between 1988 and 1999, they found that people without GB virus infection were four times more likely to die.

In a second study, German researchers found that, on average, those with the highest levels of GB virus in their blood had the lowest levels of HIV. Individuals with detectable GB virus had an average viral load 0.7 log below individuals never exposed to GB virus. The German group analysed 197 individuals, 33 of whom had GBV infection, who received care in the period between 1993 and March 2000. The authors do not explicitly report on the relationship between GB viremia and survival

after individuals started antiretroviral therapy, but do note that the relationship between GB viremia and survival continued to persist after triple combination antiretroviral therapy became available in 1996.

The German group also found that evidence of past exposure to GBV conferred protection; people with antibodies to the virus but no detectable viremia had lower rates of disease progression and lower HIV levels in the blood, although the effect was less than that seen in people with detectable GB viremia. The majority of individuals in the Hanover cohort exposed to GBV appeared to have cleared the infection: 56.0% had antibodies compared with 16.8% with detectable viremia, and the clearance rate is higher among individuals with healthy immune systems.

So far these associations are preliminary and the mechanism for any effect is unexplained. GB virus has been shown to reduce the rate at which HIV grows in CD4 cells by up to 40% when the cells are co-infected with HIV and GB virus.

References: Tillmann HL et al. New England Journal of Medicine 345: 715-24, 2001. Xiang J et al. New England Journal of Medicine 345: 707-14, 2001.

New UK guidelines

Guidelines on the use of anti-HIV treatments in people with HIV in the UK have been updated for 2001 following a consultation period. Key changes since the 1999 edition include the recommendation that treatment may be delayed until the CD4 count falls below 200. In people with a CD4 count below 350 (but above 200), treatment should be begun only if the CD4 count is falling rapidly. This change reflects growing concern over the long-term toxicity and tolerability of HAART. Initial treatment should involve an NNRTI-based regimen in preference to treatment with protease inhibitors.

The British HIV Association (BHIVA) guidelines are available on the joint NAM/BHIVA website aidsmap.com, and will be published in print shortly in *HIV Medicine*. The new guidelines will be covered in detail in next month's *ATU*, and are also the subject of October's NAM Information Forum, with special guest speaker Professor Brian Gazzard, Chair of BHIVA (see below).

Breast enlargement

Breast enlargement, sometimes called gynecomastia, has been reported in a small number of people taking HAART. Though the effect has been attributed to a range of anti-HIV drugs, including indinavir, saquinavir, d4T and more lately efavirenz, the precise cause of this problem, and who may be at greatest risk is not known. Some cases have occurred in people who also had symptoms more typical of the lipodystrophy syndrome, but again, how the two might be connected is not clear.

In a recent issue of the medical journal *Clinical Infectious Diseases*, French doctors report successful treatment of breast enlargement in people with HIV using a dihydrotestosterone (DHT) gel. DHT is a metabolite of the male sex hormone testosterone, and the substance has been used to treat breast enlargement in other patient groups.

Reference: Benveniste O et al. Clinical Infectious Diseases 2001;33:891-3.

Syphilis in Dublin

Following our coverage of the ongoing syphilis epidemic in the UK in July's *ATU*, we've been reminded that the latest information on the problem in Dublin, where there has been over 130 cases since July 2000, is available at <http://www.ndsc.ie>.

New from NAM

NAM have recently published a fully revised edition of our acclaimed *HIV & AIDS Treatments Directory*. This comprehensive guide contains A-Z sections on illnesses, symptoms, treatments, and medical tests, and overview sections on key topics such as adherence, side-effects and healthy living, ensuring you have the latest information on all medical aspects of HIV.

For further information and to order your copy please call 020 7627 3200, email info@nam.org.uk, or visit www.aidsmap.com.

In the next few months, NAM will be publishing the 2001 edition of the *AIDS Reference Manual*, a complete handbook on social aspects of AIDS, including epidemiology, HIV transmission, prevention and testing, and life with HIV. Revised editions of NAM's booklets on *Viral Load*, *Anti-HIV Drugs* and *Resistance*, plus a new title *Lipodystrophy*, are also coming soon, along with a new *Directory of Complementary Therapies in HIV and AIDS*.

October NAM forum

Our special guest speaker at NAM's Information Forum on Monday, October 22nd is Professor Brian Gazzard, Chair of the British HIV Association (BHIVA), and Research Director of London's Chelsea and Westminster Hospital. Brian will be discussing the 2001 revision of BHIVA's guidelines on the use of anti-HIV drugs for treatment of HIV.

The forum runs from 7-9pm at the University of London Union, Malet Street, London WC1. The event is free and everyone is welcome. A sign language interpreter is available.



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any questions

For an introduction to HIV treatment issues

The booklets in NAM's Information Series for Positive People are free to people with HIV. This easy-to-read series covers six key topics: Viral Load, Clinical Trials, Nutrition, Anti-HIV Drugs, Resistance, and a Glossary.

The HIV & AIDS Treatments Directory

This 600 page book, published twice a year, is a comprehensive guide to the medical aspects of HIV. Available at only £12.95 to people with HIV, £64.95 to professionals.

<http://www.aidsmap.com>

NAM's resources are also available online at [aidsmap.com](http://www.aidsmap.com). These include our extensive and searchable treatments database, the latest news on treatment developments, our online directory of AIDS service organisations, hundreds of links to recommended HIV-related sites, and free downloadable resources.

Monthly NAM information forums in London

Each month an expert speaker discusses a treatment-related topic. Entry is free. Future forums are advertised inside this newsletter.

AIDS Treatment Phonenumber 0845 9470 047

From Terrence Higgins Trust: Mon & Wed 3-9pm, Tue 3-6pm.

NAM recommends that you discuss all your treatment decisions with your doctor.



subscriptions

Free to individuals in the UK affected by HIV or AIDS.

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**AIDS Treatment Update
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