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www.aidsmap.com
issue 205 april 2011

hiv treatment update

Gus Cairns

in this issue

HIV is still complicated. In the last two decades a universally lethal illness has been transformed into an infection people can live with for a relatively normal lifespan.

Research in HIV and related conditions continues to forge ahead. On page 14 we provide an update on hepatitis C treatment, which is at the exciting stage HIV treatment was at in the early 1990s: we may be able to treat the vast majority of infections soon (though whether the NHS will fork out the £28,000 cost per person is another question). And one of the most exciting stories from February's Conference on Retroviruses and Opportunistic Infections (see page 12) was the first proof-of-concept of a gene therapy that could eventually lead to a cure for HIV.

That does not, however, mean that having HIV means everyone can pop a daily pill or two and they'll be fine.

I was reminded of this recently when I stayed at a gay B&B. One of my fellow guests was in his 50s. He'd been diagnosed with HIV ten years ago because he'd had anal cancer. He had permanent kidney damage due to the side-effects of HIV medication and the cancer chemotherapy had knocked his immune system so badly that he'd developed AIDS-defining recurrent herpes symptoms which were very hard to live with. He was very grateful to his clinicians for the care they'd given him and the complicated decisions they'd had to make to keep him alive, but it had been a very near thing, and the same man diagnosed today would present exactly the same medical care challenges.

That's why in this issue we've gone back to the clinical basics a bit. Matt Sharp covers lymphoma, another HIV-related cancer that still presents a formidable health management challenge (page 8). And as part of NAM's original, founding commitment to provide people with HIV with the information they need to make the best decisions about their health, we include David McLay's cut-out-and-keep guide to the most commonly used medical tests (see page 4); next time your doctor tells you everything is "fine" or "your cholesterol's up a bit" and you'd like to know more, you can whip it out and quiz him or her on exactly what's going on and whether to do anything about it.

One of the additional complications of HIV is how to afford it. Although we have made tremendous progress, we still live in a world where half the people who need antiretrovirals to save their lives don't get them. As we reveal on the opposite page, however, HIV treatment is also becoming increasingly difficult to afford in the UK. Health commissioners are having to make hard-nosed decisions about offering the most affordable regimen that doesn't endanger health, rather than the perfect one.

In the current situation, a truly collaborative approach to treatment between patient and doctor is more important than ever, which is why we'll keep providing the information you need. Stay well.

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hiv treatment update
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design Rowena Weedon
printing Cambrian Printers
ISSN 17567890

charity number 1011220

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about NAM
NAM is a charity that exists to support the fight against HIV and AIDS with independent, accurate, up-to-date and accessible information for affected communities, and those working to support them.

For more information, and details of our other publications and services, please contact us, or visit our website, **www.aidsmap.com**.

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upfront

HIV drug prescribing in London: changes from this month

From April 2011, the preferred first- and second-line drug regimens for HIV-positive people in London are changing. The change in prescribing practice will not initially affect people on current regimens but will be applied to new patients and to those who need to change to a second-line protease inhibitor-based regimen.

The two primary changes are:

1. The preferred first-line regimen will change from tenofovir + FTC + efavirenz to abacavir + 3TC + efavirenz. What this means in practice is that, instead of taking one pill a day (the combination pill *Atripla*), most new patients will take two (*Kivexa* [3TC + abacavir] plus *Sustiva* [efavirenz]).

2. If patients have to start on or switch to a protease inhibitor (PI)-based regimen, the PI initially prescribed will be atazanavir (*Reyataz*). Some patients taking 'old-fashioned' PIs may be offered a change to atazanavir.

These changes are due to a new two-year purchasing agreement between the London HIV Consortium (LHC) and the drug companies. The LHC represents the majority of London's hospital and primary care trusts and, since 47% of people with HIV accessing care in England live in London, has considerable negotiating power when it comes to the prices paid for drugs.

Although a maximum 'list price' is set by each country for drugs licensed in Europe, an aspect of HIV care that gets little scrutiny is that NHS bodies – ranging from individual trusts to large consortia like the LHC – negotiate their own deals with each drug supplier. The LHC has managed over the years, due to its economic position, to pay about 25% below list price for antiretrovirals.

This year, however, primary care trusts in London told the LHC and HIV prescribers that their budget would not grow this year. This meant that hospitals needed to save £9 million on drugs in order to accommodate other HIV patient and clinic costs and not to lose services. This excluded other cost-saving measures like home delivery (which is cheaper because it does not attract VAT). Although the overall HIV spend has not been cut, the number of patients continues to increase, (a 5.3% increase in 2009 in London), and thus the amount spent on drugs had to come down.

Although in terms of cost per lives saved, HIV treatment is a cost-effective intervention, its sheer cost to the NHS these days is staggering: with a higher HIV prevalence than the rest of the country, 19% of the entire London NHS drugs budget in 2009 was spent on antiretrovirals, and 29% of the budget for specialist conditions.

The changes are based on current clinical practice and no patient will be forced to take a drug with significant side-effects or which is detrimental to their quality of life. They are also in accordance with the most recent treatment guidelines issued by the British HIV Association (BHIVA),[1] although these guidelines are now three years old (new ones are planned for later this year).

They are, however, bound to cause some controversy. The biggest area of concern surrounds the use of abacavir and conflicting evidence about an increased risk of heart attack.[2,3,4,5] The difference may be due to the fact that large cohort studies like D:A:D may miss a factor that impacted on both health and choice of drug regimen.

There is also some evidence – again disputed – that abacavir may not be as potent as tenofovir in suppressing HIV in patients with a high viral load (see News, page 12).[6,7]

Because of these concerns, tenofovir instead of abacavir will be prescribed to patients with a viral load over 100,000 copies/ml or with a high heart attack risk score.

Does having to take two pills a day impact on adherence or health? One study last year found a difference between one- and two-pill regimens, but this has not been found in other studies.[8]

Atazanavir does not raise blood lipids (fats) as much as other protease inhibitors and is taken as one capsule, once a day. It has been linked to kidney stones in a few patients and can cause a harmless but sometimes marked form of jaundice; darunavir (*Prezista*) is recommended as the alternative for people who cannot tolerate atazanavir or have resistance to it.

The purchasing agreement has been signed by London's lead HIV consultants and holds until April 2013. It can be changed if new clinical evidence comes along that changes prescription guidelines, but it cannot now be altered if a company makes a new price offer.

The LHC, and its parent body the London Specialised Commissioning Group, can withhold all or part of the HIV drugs budget from any clinic seen to fail to achieve the cost savings expected, though commissioners stressed that this was a "final resort", and would be seeking to work in partnership with clinics to meet the requirements of the agreement.

For more information on these prescribing changes, see: http://i-base.info/home/changes-to-hiv-drug-prescribing-in-london/.

testing... testing... one, two, three

When you visit your HIV clinic, they will be measuring a lot more than just your CD4 count and viral load. What else are they checking and how does it matter? Guest writer *David McLay* explains.

Your doctor scans the list of indecipherable acronyms, quickly checking the boxes beside some and skipping over others. She hands the sheet to you and says "You can have some blood taken for the usual tests. Any questions?"

You say "No," but maybe you think to yourself, "Yes!" What are these tests? What do they measure? What's a good result and what's a worrying one? You shrug your shoulders and head off, hoping that this early the queue isn't too long – though you know it will be.

If you receive medical care regularly, routine visits with the doctor usually involve a set of physical and blood tests that can be bewildering. Knowing what each test measures, and which ones you should be receiving, can help you feel more comfortable and involved in your care.

Tests can monitor the function of organs or systems in the body, such as blood pressure, or can diagnose specific conditions, such as infections. In this article, we'll look at the monitoring tests most commonly performed at a routine visit to your HIV doctor and what they indicate about your health. We won't cover HIV-specific tests such as CD4 cell count, viral load, resistance testing and screening for abacavir hypersensitivity. You can find out more about these in our booklet *CD4, viral load & other tests* (details at the end of this article).

What should be monitored and why

Everyone should have the health of their major organ systems monitored from time to time, but people with HIV often have additional reasons to do so. Both HIV and its treatment increase the risk of several health issues, including blood problems, cardiovascular disease and liver and kidney damage. We are becoming increasingly aware that bone loss may also be a side-effect of HIV treatment, and a recent study suggests that changes to bone metabolism start as soon as two weeks after starting treatment.[1]

The table below outlines the tests commonly done to monitor our health. This is not a comprehensive list, and you may have other tests done, even at a routine visit. Other tests commonly performed include tests for sex hormones like testosterone and estradiol; for other hormones like the thyroid hormones; other tests of liver function like prothrombin clotting time; tests for vitamin and trace mineral deficiency; investigations such as lung function tests and chest X-rays; and any number of different diagnostic tests for specific conditions ranging from cancers to infectious diseases.

The tests: vital signs and biometrics

Temperature: So routine, we often forget to include it. The normal value quoted is 37°C, or 98.6°F.

Blood pressure: A blood pressure reading comprises two measurements: the *systolic* blood pressure (SBP), read just after the heart has contracted, and the *diastolic* blood pressure (DBP), read when the heart is relaxed and is refilling.

High blood pressure, also commonly known as hypertension, is a risk factor for cardiovascular disease. For every 20/10 mmHg rise in blood pressure, the risk of cardiovascular disease doubles.[2]

Weight, BMI and waist circumference: Weight is one measure of health, with lower- or higher-than-normal values, or dramatic changes in weight, indicating potential problems.

Wasting, which includes the unintentional loss of at least 10% of body mass over 30 days, may indicate a

potentially fatal condition. Thankfully, HIV-related wasting is much less common now that effective antiretroviral therapy is available, but wasting may indicate other conditions like tuberculosis (TB) and cancer.

Excess body fat is also unhealthy: it is linked to increased risk of death and several diseases. Some are the usual suspects, including high blood pressure, unhealthy blood lipid levels, cardiovascular disease and diabetes, while others might surprise, such as osteoarthritis, sleep apnoea and certain cancers.

Because the human body comes in many shapes and sizes, weight alone is not an adequate way to determine what is dangerous for someone. Body mass index (BMI) and waist circumference attempt to identify unhealthy mass. BMI includes height in its calculation, partially accounting for differences in body shapes.

Waist circumference (measured around the largest part of the belly) is an easy-to-measure indicator of abdominal fat and is independently associated with increased risk of death.

Blood tests

Full blood count (FBC): counts the different types of cells in your blood. There are red blood cells, which carry oxygen; white blood cells, which form part of the immune system and defend us from infection; and platelets, which help the blood to clot. Blood counts are used to diagnose and monitor several diseases and conditions, including anaemia, infections, inflammatory diseases and cancers.

The red blood cell count includes the number of red blood cells, the total amount of the oxygen-carrying molecule haemoglobin and the amount of space red blood cells fill in blood, called haematocrit.

Women generally have fewer red blood cells than men. Anaemia, a deficiency of red blood cells, indicates a clinically significant drop in the ability of blood to carry oxygen. Anaemia is not a disease, but rather a symptom, which may indicate a condition that needs to be investigated.

The white blood cell differential count measures five subtypes of white blood cell. These are:

- **Neutrophils**, which mobilise a quick response to infection
- **Lymphocytes**, which co-ordinate a more sophisticated set of responses and 'remember' infections
- **Monocytes**, which target and destroy invading pathogens and foreign matter
- **Eosinophils** and **basophils**, which target parasites and mount allergic reactions.

The familiar CD4 cell count measures a subset of the lymphocyte family of cells. A decrease in white blood cell counts indicates an immune dysfunction – the kind seen in AIDS is only one of several types – while an increase may be caused by an infection or tumour. Increases in the different subtypes of white blood cells can be a clue to the underlying problem.

Platelets are cell fragments involved in blood clotting. Having too few platelets increases the risk of uncontrolled bleeding, while having too many increases the risk of excessive clotting, which can cause the blockages that lead to a cardiovascular crisis such as a stroke or pulmonary embolism (a blood clot in the lung).

Blood chemistry: measures the electrolytes (salts) chloride, potassium and sodium, bicarbonate (dissolved carbon dioxide), glucose, creatinine and urea. It often also measures calcium and the protein albumin. These tests monitor kidney function, blood acidity, and levels of electrolytes and sugar. Abnormal levels are generally a sign of other underlying conditions and warrant investigation.

The protein albumin is the most abundant protein in blood, and acts like a sponge to soak up excess fluid. Decreases in albumin are associated with liver damage and a form of kidney disease. They also occur when the body goes into shock or is experiencing severe inflammation. Results from other tests distinguish between the potential causes.

Creatinine is a waste product of muscle metabolism. Because the kidneys are responsible for almost all removal of the compound from the body, blood creatinine levels are a good indicator of kidney function. Creatinine levels can be used to calculate the 'estimated glomerular filtration rate' (eGFR), which takes account of the age, sex and ethnic origin of the person. A high blood creatinine level and a low eGFR indicate kidney damage and decreased kidney function.

Levels of specific electrolytes may be abnormal in specific disorders. Diabetes,

The most common tests

Blood health	Full blood count
Cardiovascular health	Blood glucose Blood pressure Lipid profile Weight, BMI and waist circumference
Liver health	ALT/AST ALP Bilirubin Albumin
Kidney health	Blood chemistry (urea and electrolytes, creatinine) Estimated glomerular filtration rate (eGFR) Urine dipstick analysis (protein)
Bone health	Blood chemistry (calcium) DEXA Vitamin D

kidney damage, some forms of heart disease and muscle and nerve problems can all result in electrolyte imbalances. Prescription drugs may also change levels. Other signs and further testing can determine the condition that is causing imbalance.

Levels of blood sugars (also called blood glucose) are used to monitor for signs of diabetes or its precursor, insulin resistance. Diabetes, if left untreated, can lead to serious issues such as cardiovascular disease, kidney damage, increased risk of problems with feet and legs, and damage to the eyes.

Blood for a glucose level test is often drawn after you have fasted; that is, not eaten for at least eight or nine hours. This avoids the fluctuations in glucose levels that occur after eating and provides the most accurate measurement. If results suggest a problem, your doctor is likely to order a more specific test, called an oral glucose tolerance test, that evaluates the body's ability to control blood glucose levels.

Lipid profile: Blood tests for fats (also called lipids) measure levels of cholesterol and triglycerides. The two forms of cholesterol of interest are low-density lipoprotein (LDL or 'bad' cholesterol) and high-density lipoprotein (HDL, or 'good' cholesterol). Tests will also measure total cholesterol, as well as another type of fats called triglycerides. Generally, levels of total cholesterol and triglycerides should be as low as possible and so should your LDL:HDL ratio. Unhealthy levels of blood lipids are a risk factor for cardiovascular disease.

Liver function tests: ALT (alanine aminotransferase) and AST (aspartate aminotransferase) are two enzymes found within cells of the liver. Their presence in the blood indicates damage to the liver cells. Results are likely to vary from test to test and so dramatic changes, often presented as multiples of your 'normal' reading, are a more reliable indicator of ongoing damage. A change that is up to five times a normal reading is considered mild impairment.

If levels of either enzyme, or their ratio (ALT:AST), change, your doctor is likely to look for indications of potential causes. These could include viral hepatitis infections, starting to take certain antiretroviral or other prescription drugs, drinking a lot of alcohol, being obese, having insulin resistance or diabetes, or having high blood lipid levels.

Alkaline phosphatase and total bilirubin are two other liver tests that may be ordered. Elevated levels of either may be a sign of liver damage or another condition and so results are interpreted along with other liver function test results. One HIV drug, atazanavir (*Reyataz*), causes a type of rise in bilirubin levels which is usually harmless.

Vitamin D: is not routinely measured but 25-hydroxyvitamin D, the form measured in a blood test, may be, as part of monitoring bone health. Extremely low levels of the vitamin may be associated with bones that do not mineralise (or harden) while more-than-mild deficiency may be linked to osteoporosis (low levels of calcium in the bone, which leads to weakness and fractures). Deficiency has recently been found in a large proportion of people with HIV from diverse geographical regions.[3] There is no evidence as yet that supplementing mildly depleted levels of vitamin D is of benefit, but as it's a cheap supplement, doctors may prescribe it.

Calcium: levels may also be related to bone health, but are only useful diagnostically in cases of severe bone disease. Low calcium may indicate kidney failure or a number of other conditions.

Other tests

Urine dipstick analysis: Testing the chemical composition of urine can detect metabolic and kidney disorders and infections of the urinary tract. Analysis is usually performed using test strips that contain small test pads for each compound of interest. The strips are dipped in the urine sample and colour changes in the pads indicate the results. The most common chemical tests include pH (blood acidity), protein, glucose, ketones, blood, nitrite and bilirubin.

The presence of a compound not normally found in urine is a sign of an underlying disorder. Albumin in the urine can be an early sign of kidney damage, while blood in the urine may suggest internal injury, kidney stones or cancer. Bilirubin in urine can be a sign of liver damage. Glucose and ketones (produced by the liver as part of fatty acid metabolism) are signs of diabetes. The presence of nitrite is a sign of bacterial infection.

DEXA: Dual-energy X-ray absorptiometry (DEXA) is a non-invasive procedure for measuring bone mineral density. Low bone mineral density (called osteoporosis in severe cases) is associated with an increased risk of bone fracture.

DEXA scans are not performed routinely as they are expensive, but will be if osteoporosis is suspected. Scans can be performed of the hip or the spine and results are reported as T-scores or, less commonly, Z-scores. A T-score compares your test result to the bone density of a 'young, normal' person of the same sex and is used to diagnose osteoporosis. A Z-score compares your test result to the result of a typical person of your age and sex.

Both scores measure the difference between the reference result and your result using a statistical concept called standard deviations. For example, a T-score of -1.7 indicates that your score was 1.7 standard deviations below the reference score. This means that 92.4% of the population has a score higher than yours. A T-score below -2.5 (lower than 99.4% of the population) is diagnostic for osteoporosis, while a T-score between -1 (lower than 68% of the population) and -2.5 is considered low bone mass, or osteopenia.

Risk assessment tools

In addition, there are two risk assessment tools used to monitor the health of specific organ systems.

Cardiovascular health: The Framingham risk assessment tool is widely used to calculate the risk of a heart attack or death due to heart failure over the next ten years. The tool incorporates many of the traditional risk factors for cardiovascular disease: age, sex, smoking, high blood lipid levels and high blood pressure. The Framingham tool was developed in HIV-negative people, but a similar tool specifically for HIV-positive people is in development.

Bone health: The FRAX questionnaire assesses the risk of fracture and whether a DEXA scan is appropriate. The tool applies to people older than 40; it may underestimate the risk of fracture in people with HIV.

Tests and their 'normal' ranges

A 'normal' range is not set in stone, and may change as new research comes along. You may find some sources quote rates slightly different from the ones opposite. Do not worry if you are a couple of decimal points outside the limits.

The body keeps some substances, such as glucose, within narrow limits so results significantly outside these are indicative of trouble. In other cases, such as liver enzymes, only results considerably in excess of the normal range matter.

Test results are, confusingly, expressed in two different systems of units: SI (*système internationale*) units, which are modern metric-system units, and which are generally the ones used in UK health care, and US units (often called 'conventional' units in the US), which still appear in many scientific papers. ■

Want more information?

You can find out about the most common (and some less common) tests and examinations you will have as part of your routine HIV care in NAM's booklet, *CD4, viral load & other tests*. NAM provides extensive information about HIV, related health conditions, and their monitoring and treatment.

Check out www.aidsmap.com for news stories, fact sheets and previous editions of *HTU*.

www.labtestsonline.org.uk provides more information on a wide range of medical monitoring tests.

Tests and normal ranges

Test		Normal or optimal values	
		SI units	Conventional (US) units
Body temperature		37°C	98.6°F
Blood pressure	Systolic	120 to 129 mmHg	
	Diastolic	80 to 84 mmHg†	
Body mass index		18.5 to 24.9 kg/m²††	
Waist circumference	Men	< 94 cm (UK)†††	< 40 in (US)†††
	Women	< 80 cm (UK)†††	< 35 in (US)†††
Complete blood count[4]			
Red blood cells*	Men	4.3 to 5.9 trillion/l‡	4.3 to 5.9 million/mm³‡
	Women	3.5 to 5.5 trillion/l‡	3.5 to 5.5 million/mm³‡
Haemoglobin*	Men	2.09 to 2.71 mmol/l	13.5 to 17.5 g/dl
	Women	1.86 to 2.48 mmol/l	12.0 to 16.0 g/dl
Haematocrit*	Men	0.41 to 0.53	41 to 53%
	Women	0.36 to 0.46	36 to 46%
White blood cells		4.5 to 11.0 billion/l‡	4500 to 11,000/mm³
WBC subtypes	Neutrophils	55 to 70%	
	Lymphocytes	20 to 40%	
	Monocytes	2 to 4%	
	Eosinophils	1 to 4%	
	Basophils	0.5 to 1%	
Platelets		150 to 400 billion/l‡	150,000 to 400,000/mm³
Lipids			
Total cholesterol		< 5.2 mmol/l	< 200 mg/dl
LDL cholesterol		< 2.6 mmol/l	< 100 mg/dl
HDL cholesterol		> 1.0 mmol/l	> 40 mg/dl
Triglycerides		< 1.7 mmol/l	< 150 mg/dl
Blood chemistry**			
Bicarbonate (CO_2)		22 to 29 mmol/l	22 to 29 mEq/l
Calcium		2.15 to 2.55 mmol/l	8.6 to 10.2 mg/dl
Chloride		95 to 108 mmol/l	95 to 108 mEq/l
Potassium		3.5 to 5.3 mmol/l	3.5 to 5.3 mEq/l
Sodium		133 to 146 mmol/l	133 to 146 mEq/l
Albumin		35 to 50 g/l	3.5 to 5.0 g/dl
Creatinine		70 to 123 mmol/l	0.8 to 1.4 mg/dl
Glucose (fasting)		3.6 to 6.0 mmol/l	65 to 108 mg/dl
Urea		2.5 to 7.8 mmol/l	7 to 22 mg/dl
eGFR		60 ml/min	
Liver function tests**			
ALT		1 to 21 U/l (international units)	
AST		7 to 27 U/l	
ALP		50 to 160 U/l	
Bilirubin (total)		< 17.1 µmol/l	< 1.0 mg/dl
25-0H vitamin D ***		62 to 200 nmol/l	25 to 80 ng/ml
DEXA		-1 to +1 SD	

Notes

† Usually expressed as both units, e.g. "120 over 80"

†† A BMI over 30 kg/m² indicates obesity

††† These are not direct conversions: UK and US guidance differ on the threshold to health risk. In inches, the UK limits normally quoted are 37" in men and 31.5" in women.

‡ One trillion is usually expressed as 10^{12}, a billion as 10^9, and a million as 10^6.

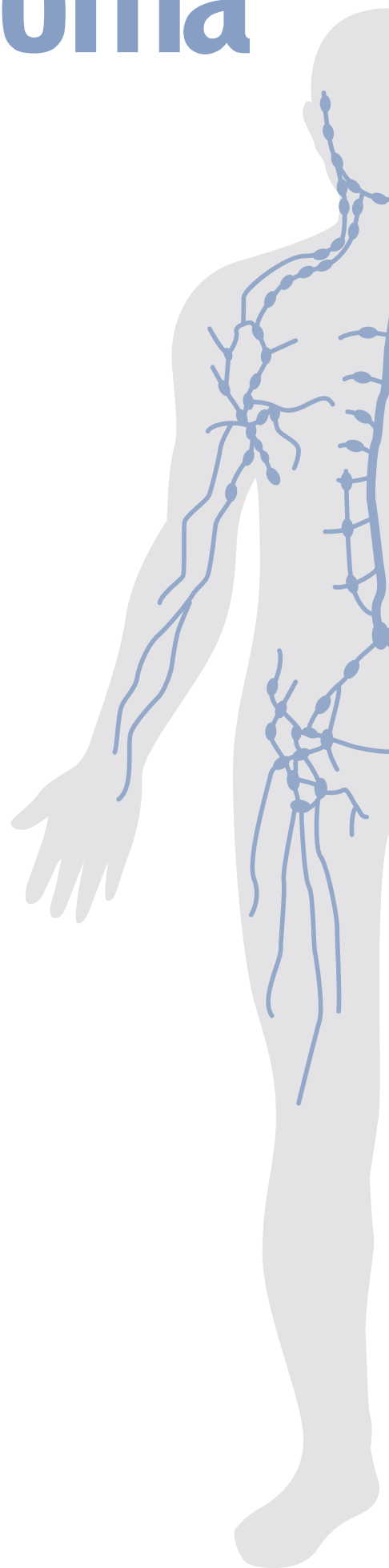
* normal ranges vary with altitude

** reference values vary from lab to lab; these values provided only as a general guide

*** normal range varies with ethnic background, age, geographic location and sampling season

hiv and lymphoma

Guest writer *Matt Sharp* updates *HTU* on a group of cancers that still cause premature deaths in people with HIV, though cure rates are improving.



The 'C' word

Tim Horn is now president of aidsmeds.com, a US-based HIV information website. In 1997, he was very unwell. He soon discovered he had a type of cancer called lymphoma.

> "*I'd had night sweats, low-grade fevers and diarrhoea, which felt totally out of the ordinary. Blood tests showed sharp elevations in two markers: uric acid and lactate dehydrogenase.*

> "*My doctor had the good sense not initially to say the 'C' word, but I figured he was looking for something sinister when he arranged an immediate CT scan. Forty-eight hours later, he called and said that there were two masses near my large intestine and that I should definitely see an oncologist [cancer specialist]. After several more investigations, I was diagnosed with non-Hodgkin's lymphoma.*"

In the beginning of the AIDS epidemic, lymphoma often showed up in those with very late-stage HIV and was usually terminal. Non-Hodgkin's lymphoma (NHL), the AIDS-defining variety, was responsible for one-in-six AIDS deaths.[1] Today, antiretroviral drugs, chemotherapy and other new treatments help to make this a disease that can be overcome. It's important from the start, however, to acknowledge that lymphoma is still a life-threatening illness: the sooner it's diagnosed and treated, the better.

Definitions

Lymphoma means cancer of the lymphocyte cells of the immune system, and usually shows up in the lymph nodes first (in contrast to other immune-system cancers like leukaemia), although other parts of the body may also be affected. It is a complicated malignancy to diagnose and treat, and expertise in both HIV and lymphoma are important in achieving the best outcomes.[2]

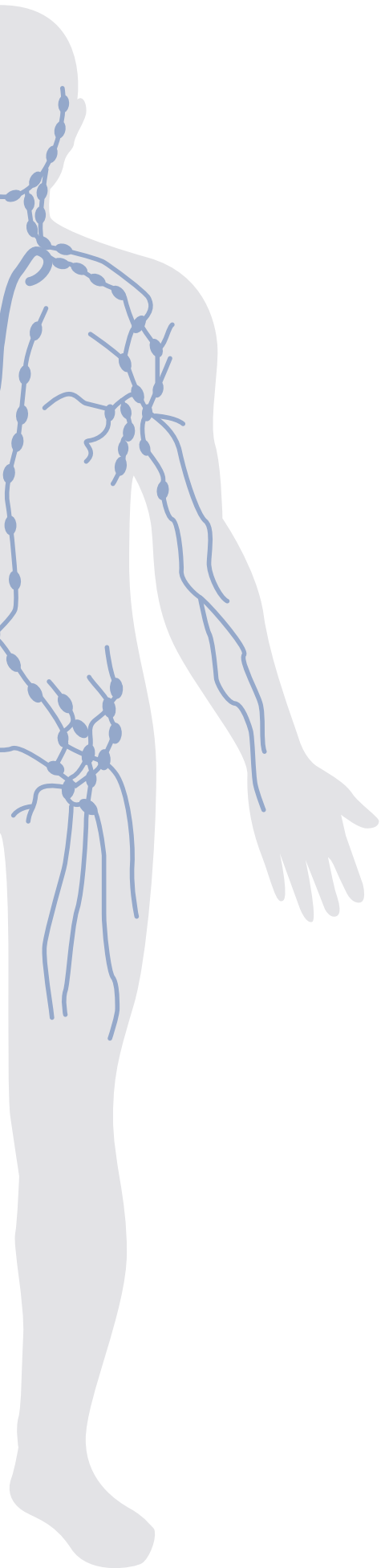
There are a number of different types of lymphoma, differentiated by the type of cells affected, the type of cancer cells they develop into, and the way the cancer spreads.

Hodgkin's lymphoma (or Hodgkin's disease) is characterised by the development of cancer cells called Reed-Sternberg cells, which normally develop from the B-lymphocytes, the cells originating in the bone marrow that secrete antibodies. Hodgkin's tends to spread slowly through the lymph vessels from one lymph node to the next and doesn't present in non-lymphatic organs till very late-stage illness (which is, unfortunately, when it is sometimes diagnosed). Hodgkin's lymphoma is not an AIDS-defining illness.

Every lymphoma that isn't Hodgkin's lymphoma is classed as **non-Hodgkin's lymphoma (NHL)**. Eighty per cent of this category consists of a type of cancer called diffuse large B-cell lymphoma. But it includes several rarer cancers such as Burkitt's lymphoma, a very aggressive lymphoma, which occurs in 16% of cases of NHL in people with HIV, as opposed to 2% in the general population.

It also includes primary central nervous system lymphoma, an often quickly lethal form of brain tumour. This used to occur in up to 10% of people with AIDS, usually at a CD4 count of less than 50, but the incidence has dropped off significantly, even compared to other lymphomas, in recent years and it is now a rare AIDS-defining illness.

Up to 30% of NHL types are still to be named; categories are based on what reference laboratories have been able to identify thus far and not all lymphomas fit comfortably into a type.



What causes lymphoma?

Epstein-Barr virus (EBV), the same virus that causes infectious mononucleosis (glandular fever) causes the majority of NHL and all cases of Hodgkin's lymphoma occurring in people living with HIV. There's little point in trying to avoid EBV: 95% of adults have been infected with it at some point, usually without symptoms. High concentrations of EBV are found in lymphoma cells.

EBV used to be known as human herpes virus 4 (HHV-4). A similar virus, HHV-8, also known as KSHV, is the virus that causes the AIDS-defining cancer Kaposi's sarcoma and is also very occasionally the cause of NHL in people living with HIV.

Current research is studying lymphoma pathogenesis, why it is a continuing problem, even in otherwise healthy HIV-positive people, and why EBV triggers cells to become cancerous in some people but not others.

How common is it?

NHL in people with HIV has become less common in the era of combination therapy, although its incidence has not declined as fast as other AIDS-defining cancers, so it is responsible for a higher proportion of deaths than it used to be. A Swiss HIV Cohort study from 2008[3] found that the annual incidence of NHL had declined from 1.36% before combination therapy to 0.18% a year in 2002-2006 (one case per 555 patients a year). It is still 23 times more common in people with HIV than in the general population.

In contrast, Hodgkin's lymphoma has become more common in people with HIV. In one US cohort study, the annual incidence of Hodgkin's lymphoma was 0.5% a year in people diagnosed with AIDS (as opposed to HIV) between 1996 and 2006 and was actually less common in people with low CD4 counts than in people with high CD4 counts.[4] Its incidence rate increased threefold during this time and it is about ten times more common in people with HIV than in the general population.[5]

Prognosis

Tim Horn wondered how he could be diagnosed with an AIDS-defining illness with a CD4 count of 450.

> *"[I was] devastated because I knew that NHL survival in people with HIV was a coin toss in the late '90s – a 50% chance of death within a year – compounded by a rather cinematic idea of what cancer illness and treatment would be like."*

NHL is cured in 40 to 50% of cases with standard chemotherapy. One study of incidence and mortality due to lymphoma since HIV combination therapy was introduced in 2006 found that more than half (59%) of HIV-positive patients with NHL died within two years of diagnosis, compared with 29% of HIV-negative NHL patients; having HIV was associated with a nearly sixfold increase in two-year mortality.

Antiretroviral therapy has had a substantial impact on NHL specifically, and is recommended today as a part of the overall treatment and management of both diseases, but NHL remains a serious illness.

The addition of newer anti-cancer agents such as rituximab (*Rituxan* or *MabThera*), however, has increased two-year survival rates to 75% or more.[7] Hodgkin's lymphoma is generally less aggressive, with a two-year survival rate of one group of patients of 81%.[8]

Fifty-four per cent of people with HIV and Hodgkin's lymphoma have an undetectable viral load. It is speculated that the immune reconstitution caused by HIV treatment may actually provide the particular kind of immune stimulus for EBV to proliferate and/or for lymphoma cells to grow and become cancerous in response to its proliferation.

A European study (COHERE) followed people with HIV to see how many would develop Hodgkin's lymphoma despite antiretroviral therapy. Hodgkin's incidence was similar in people who were either on or off antiretroviral drugs, but CD4 cells dropped sharply before the diagnosis of Hodgkin's in people on therapy, despite their having an undetectable viral load. This may be a useful indicator to watch for. Conversely, people diagnosed with NHL did not experience such a decrease in CD4 cells prior to diagnosis.

Symptoms

Most often, lymph node swelling is the main symptom in the majority of lymphomas. The node will be hard, immobile or barely mobile, and painless.

B-symptoms are a group of classic symptoms that may be present in people with lymphoma, typical of many other infections because they are a part of the immune response. These include fever, night sweats and weight loss, and are found in 60 to 80% of cases. Weakness, tiredness and rapid physical deterioration are common.

Non-Hodgkin's lymphoma is more likely to produce systemic (non-local) symptoms than Hodgkin's lymphoma.

Every part of the body may be involved, but the gastrointestinal tract, liver and bone marrow are affected frequently so bone pain, internal bleeding and abdominal pain may be involved. Headache without fever is the primary symptom with central nervous system involvement. A combination of many of these symptoms may be expected in all types of lymphomas.

Diagnosis

It's important to follow up any suspicion of lymphoma as soon as possible, as earlier detection leads to better outcomes. A lymph node biopsy should be performed as soon as possible, done by a specialised lab with experience in identifying lymphomas. This is a small operation, usually done under a general anaesthetic.

Patients will generally have blood tests and a chest X-ray as well, in part to check on their general health. If the biopsy shows the presence of a lymphoma, there will be further tests to see if the disease has spread to other parts of the body. These could include scans, ultrasound examinations and bone-marrow biopsy.

Diagnosis of a lymphoma should include identifying its subtype, to determine how the particular cancer cells multiply and the markers that are expressed on the cells. All this information is needed for an appropriate treatment recommendation.

In any cancer, *staging* is crucial to determine how far along the tumour has progressed. The Ann Arbor classification system for lymphomas rates stages from I to IV (I being the least progressed), and there is a subdivision of categories known as symptomatic and asymptomatic.

Abdominal ultrasounds, CT scans and bone marrow biopsies are all important diagnostic tools. In people with HIV, CD4 count, viral load, blood counts, inflammation markers, uric acid, liver and kidney markers, and electrolyte levels must also be assessed. Cardiac function must also be checked because some chemotherapy agents are toxic to the heart.

Treatment and new directions

Tim's treatment was aggressive.

> "*Treatment for me began with a bang. As I wasn't on HIV treatment, I needed to start immediately which was bad enough by itself at the time.*
> *I had to start two different types of chemotherapy: a month of spinal infusions of cytarabine [see glossary] to treat the (possible) cancer in my bone marrow and to prevent it from migrating to my brain, and full-dose CHOP [see glossary], delivered in 21-day cycles.*"

Hard-hitting and early treatment is necessary since lymphomas often progress rapidly. It can sometimes take too long to determine the stage of the illness to wait for this information before starting treatment. Every HIV lymphoma should be treated first with chemotherapy with the intention of achieving remission (halting or reversal of the progression of cancer). Surgery or radiation alone are not sufficient.

Treatment for NHL

In Europe, CHOP chemotherapy is recommended [see glossary]. Antibiotics are usually added as chemotherapy reduces white blood cells, key to fighting infections. Chemotherapy can cause a sore mouth; mucous membranes in the mouth can be treated with mouthwashes and the antifungal drug amphotericin prescribed for topical use if a patient develops fungal thrush. Filgrastim (G-CSF) can be prescribed to avoid developing dangerously low white blood cell levels (neutropenia).

Three out of the four CHOP drugs have to be administered by drip but patients can be trained to hook themselves up at home, or have visits from a cancer nurse from an organisation like Macmillan to help. EPOCH [see glossary] may be considered as an alternative, but the additional drug, etoposide, needs to be administered to patients in hospital as it may cause sudden falls in blood pressure if administered too fast.

There is a distinct trade-off between toxicity and effectiveness in many of these regimens. Most of the side-effects of CHOP and other lymphoma regimens are generic to cancer chemotherapy: hair loss, nausea (sometimes intense), skin irritation, pain at the infusion site, and increased vulnerability to other infections. This is because drugs that stop cancer cells growing are blunt instruments and will tend to damage healthy immune-system cells too.

In people living with HIV who are then diagnosed with NHL, there is no question that they should start antiretroviral therapy as soon as possible, if they are not already on treatment: in one study from 2001, the two-year survival rate of patients with HIV treated with antiretrovirals and CHOP was 75% compared with 34% of patients on CHOP alone.[9]

Mortality rates are still higher amongst HIV-positive patients with non-Hodgkin's lymphoma than in HIV-negative people with the cancer, but having a higher CD4 count (and not having had a previous AIDS-defining illness) reduces the risk of death.[10] Several studies show positive outcomes and there are cases in which complete remission is seen, even without chemotherapy.[11] Some ARV drugs should be avoided, especially AZT, as they can damage bone marrow and create immune suppression itself.

Rituximab (*Rituxan* or *MabThera*) is a drug that is becoming more common in lymphoma chemotherapy. It adds effectiveness and length of response compared to conventional chemotherapy and is commonly administered in conjunction with standard chemotherapy. Rituximab is an antibody that attaches itself to and destroys only the B-cells that are the ones that become cancerous in most types of lymphoma, but because it also attacks healthy B-cells and may cause a longer-lasting B-cell depletion, it

may lead to severe deficiency of a type of immune cell called neutrophils. One randomised controlled study of rituximab in patients with HIV who were also given EPOCH and therapies to control side-effects achieved a two-year remission rate of 75% compared with 55% without rituximab.[12]

Burkitt's lymphoma is so challenging that more intensive regimens are tried. These are often highly toxic and may require hospital monitoring. Poorer immune status or opportunistic infections do not necessarily need to impede treatment. Aggressiveness is key since standard chemotherapy usually fails. At the 2011 Conference on Retroviruses and Opportunistic Infections (CROI), a study was presented showing a two-year remission rate of 81% in patients in Spain and Germany, using chemotherapy based on methotrexate, one of the oldest cancer chemotherapy drugs, in combination with rituximab, cytarabine and another anti-cancer drug, ifosfamide.[13] However, methotrexate is a hard-to-tolerate drug, and patients experienced considerable toxic effects including profound immune suppression, bleeding and painful inflammation of the mucous membranes.

Treatment for Hodgkin's

In Hodgkin's lymphoma, different chemotherapy regimens are recommended. Most commonly, either a regimen known as ABVD is used (adriamycin, bleomycin, vinblastine and dacarbazine, an intravenous infusion), or ChlVPP (a combination of chlorambucil, vinblastine, procarbazine and prednisolone – the vinblastine is given intravenously, and the remainder of the drugs as tablets to be taken at home). Some oncologists are using a different chemotherapy strategy known as BEACOPP, developed by the German Hodgkin Study Group, although it is more toxic.

One of the most radical treatments tried for lymphoma is autogenic stem cell transplantation. Before cancer chemotherapy, stem cells from the patient's bone marrow are harvested and grown in culture. They are then reintroduced after chemotherapy, with the hope that they will grow and mature to become a cancer-free population of lymphatic cells. In one study, 56% of HIV-positive patients who had had lymphoma were alive and with no signs of relapse nearly three years after diagnosis.[14] This technique is similar to the technique used to cure HIV in the 'Berlin patient' case we have covered in previous issues of *HTU*, though in this case the stem cells re-introduced are the patient's own, not someone else's.

Conclusion: life after lymphoma

A lot of this may sound scary and grim but, as with a lot of cancers, survival rates after most kinds of lymphoma have improved markedly even since Tim Horn had his own brush with the disease and, with many new cancer therapies under investigation, will continue to do so. We'll leave the last words to Tim:

"*Though I wouldn't wish the experience on anybody I do know two things.*

"*First, lymphoma is survivable, and we've come a very long way in treating it and managing side-effects since I was diagnosed in 1997.*

"*Second, forget about what you think you know about what it means to be diagnosed and treated for any type of cancer. It is a disease, like so many others, that can be managed for years and, fortunately, cured in a number of cases.*

"*In the event of a cancer diagnosis, draw upon what you already probably know as a person living with HIV. Put yourself first; fight for dignified, expert and professional health care; understand your treatment; draw upon the support of friends and family; and live every day like it matters.*" ■

Glossary

Lymphatic system
A system of vessels in the body that regulate the fluid in tissue, distribute fats to cells, and act as the main transporters on immune-system cells – and cancer cells in people with cancer.

Lymph nodes
A set of small bean-shaped organs found throughout the body that filter foreign matter, analyse it for possible harm, and serve as garrisons and training grounds for immune cells.

Lymphoma
Cancer of the lymphatic system and especially the lymph nodes, in which the immune cells within become cancer cells.

Hodgkin's lymphoma (or **Hodgkin's disease**) A specific kind of lymphoma usually restricted to the lymph nodes, characterised by a particular kind of cancer cell, and spreading slowly from one node to the next. Not AIDS-defining.

Non-Hodgkin's lymphoma (NHL)
All other kinds of lymphoma: characterised by different cells becoming cancerous, and involvement of other parts of the body, which may be widely separated. AIDS-defining in people with HIV.

Cytarabine
Cytosine arabinoside, a nucleoside analogue drug used to fight NHL.

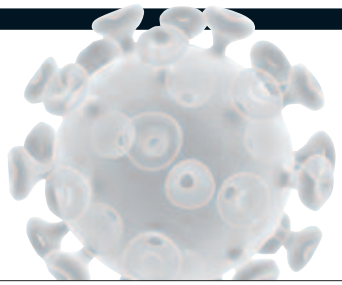
CHOP
A regimen of four anti-cancer drugs used as standard therapy for lymphoma: cyclophosphamide, adriamycin (hydroxydaunorubicin), vincristine (*Oncovin*), and prednisolone. It is given in four to six cycles of three to six weeks each. All are administered intravenously, except prednisolone.

EPOCH
CHOP plus one other drug, etoposide.

Filgrastim
Also called G-CSF (granulocyte colony stimulating factor), this is a naturally-occurring immune stimulant protein which can now be manufactured artificially and is used to strengthen parts of the immune system damaged by cancer chemotherapy.

Rituximab
A monoclonal antibody drug now used as an addition to CHOP and EPOCH, it seeks out and destroys cancer cells expressing a particular growth signal.

news from croi



Gene therapy

Patients have cells 'HIV proofed' in first step to a cure

Five US patients have had a proportion of their CD4 cells made immune to infection with the strain of HIV they have.[1]

The therapy, which could be the first step towards a cure for HIV infection, produced significant CD4 count increases in people with persistently low counts, changing their immune system to one more like that of someone without HIV.

Jay Lalezari and colleagues used enzymes called zinc finger nucleases to disable the gene producing CCR5, a molecule on the surface of some immune cells. HIV-1, the most common type of HIV, can only infect a cell with CCR5 molecules.

T-cells, an immune cell type that includes CD4 cells, were removed from six people, and infected in the test tube with an artificial virus containing zinc finger nucleases, which physically 'snipped out' the CCR5 molecule. The T-cells were re-introduced into the patients. After 90 days, up to 7% of CD4 cells showed the CCR5 deletion.

The altered CD4 cells embedded and reproduced similarly to normal T-cells. Five people experienced significant, sustained CD4 increases, averaging about 200 cells/mm^3.

The CD4 to CD8 cell ratio, typically reversed in people with HIV, normalised in five participants.

All six were on HIV treatment. The next study will try the approach with people not on treatment to see if making T-cells resistant to infection will break the chain of viral production and reduce HIV viral loads.

If this happens, protected cells would proliferate while susceptible cells would be infected with HIV and die. This could lead to a 'functional cure', at least in people who only have virus that links to CCR5.

Anti-HIV drugs

Abacavir works less well in patients with low CD4 counts

A study presented at CROI was a head-to-head comparison of treatment failure rates in patients taking abacavir/3TC (*Kivexa*) as first-line therapy and tenofovir/FTC (*Truvada*). It found *Kivexa* had a higher treatment failure rate in patients starting with high viral loads, low CD4 counts, or both, whereas all patients did equally well on *Truvada*.[1]

This study is important because tenofovir, either alone (*Viread*), as *Truvada* or, with efavirenz, as the one-pill *Atripla*, is the most widely prescribed HIV drug in the developed world. For cost reasons, however, London's HIV commissioners have decided to start new patients on *Kivexa* (see *Upfront*, page 3) unless contra-indicated.

Some studies have found that people taking abacavir are more likely to have heart attacks, though others disagree; other studies have found that people with high viral loads (over 100,000 copies/ml) are less likely to see their viral load fall to an undetectable level.

The A5202 study put 1857 people new to therapy on either *Kivexa* plus a placebo *Truvada* pill or on *Truvada* plus *Kivexa* placebo (also randomising them to efavirenz or atazanavir).

Average CD4 count on starting was 230 cells/mm^3, with 43% having a CD4 count below 200 and 18% below 50. Average viral load was 50,000 copies/ml and 25% had over 100,000 copies/ml.

Broadly speaking, treatment failure rates in patients on *Truvada* were similar regardless of CD4 count or viral load. In contrast, rates in patients on *Kivexa* differed across treatment arms. They were similar to rates with *Truvada* – approximately 20% – in people with viral loads below 100,000 copies/ml and CD4 counts over 50 cells/mm^3; only these people should be prescribed *Kivexa* under the new London arrangements.

Failure rates were higher, however, in people with baseline viral loads over 100,000 copies/ml, averaging 25% in those with CD4 counts over 50 cells/mm^3. A new finding was especially high failure rates with *Kivexa* in people who started with a CD4 count below 50 cells/mm^3, regardless of viral load (35 to 40%) – so 2.44 times higher than people with CD4 counts above 50.

In analysis that took account of factors like age and race, *Kivexa* patients with CD4 counts under 50 remained 75% more likely to fail treatment, although this became just statistically non-significant.

Anti-HIV drugs

New drug targets first step in infection

Research continues into new classes of anti-HIV drugs. CROI heard initial results from trials of BMS-663068, an attachment inhibitor.[1]

HIV infection has three stages. The virus catches hold of the CD4 molecules on immune cells. It then draws closer to the cell surface and links with co-receptor molecules (CCR5 or CXCR4). Finally, it fuses with the cell membrane and releases genetic material into the cell. The drug maraviroc (*Celsentri*) targets the second step and T-20 (enfuvirtide, *Fuzeon*) inhibits the third. BMS-663068 is a CD4 blocker, preventing the first step. It binds to a glycoprotein (gp120) in the HIV-1 'envelope', interfering with its attachment to the CD4 receptor.

For coverage of the 18th Conference on Retroviruses and Opportunistic Infections visit **aidsmap.com/croi2011**

The first study of the drug involved 50 people with clade B HIV. They had average CD4 counts of 432 cells/mm^3 and viral loads of at least 5000 copies/ml. About two-thirds were treatment-naive; the other third had been off HIV treatment for at least eight weeks.

BMS-663068 produced forty- to sixty-fold declines in viral load over the eight days of the study, and CD4 cell gains ranging from 28 to 106 cells/mm^3.

Results indicated it could be taken once a day and that ritonavir boosting was unnecessary. The most frequent side-effects were headache and skin rash, mostly mild.

Behaviour change

Does diagnosis change risk behaviour? Studies disagree

Two studies presented at CROI found that gay men diagnosed with HIV reduced the amount of sex they had that could pass on infection. Although one study (from San Francisco)[1] found that the reduction in risk behaviour was profound and long-lasting, the other (from Amsterdam)[2] showed it was comparatively slight and short-lived.

The Amsterdam study followed 206 gay men, monitoring the sexual risk behaviour of those who acquired HIV for four years before and four after diagnosis. The San Francisco study followed the risk behaviour of its 237 subjects from the date of diagnosis, for 12 years.

In Amsterdam, HIV diagnosis produced an immediate but relatively slight fall (25%) in unprotected anal intercourse (UAI). The proportion of men having UAI in the previous year was 61% four years before diagnosis, 72% at diagnosis and 53% one year post-diagnosis – but back to 61% four years after diagnosis.

The San Francisco study, counting the number of partners men had had in the previous three months, presented an apparently very different pattern: ten at diagnosis; declining to seven two years later; 8.5 after five years; then declining again (3.5 ten years after diagnosis).

This study also measured unprotected *insertive* anal sex (UIAI – most likely to pass on HIV). The number of partners of negative or unknown status with whom men had UIAI declined from 1.8 at baseline to 0.57 after a year and only 0.14 after five years.

The researchers calculated that, without taking viral suppression into account, the San Francisco men reduced the risk of passing on HIV by 71% a year after diagnosis, 87% two years later, and 92% after five years.

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we're getting there: towards a comprehensive hepatitis C cure

Research on new cures for hepatitis C has made rapid progress, *Gus Cairns* reports.

The first hepatitis C protease inhibitors, Merck's boceprevir and Vertex's telaprevir, are being reviewed by the US Food and Drug Administration and may be licensed for treating hepatitis C patients (those without HIV) by September. These drugs double to triple the likelihood of a cure in previously untreated people when taken with standard therapy (pegylated interferon and ribavirin) – and may halve the duration of treatment.

For people co-infected with hepatitis C and HIV, early results from a trial of telaprevir were unveiled recently, showing that their early viral suppression rates were just as good as in patients without HIV.

In results announced in October, interferon-free regimens comprising two new drugs achieved large reductions in hepatitis C viral load in mono-infected people. Although these results were often not sustained, due to rapid development of resistance, they suggest that, in the future, combination therapies that dispense with interferon injections may be possible.

A host of other drugs are being developed for hepatitis C. We may, in a few years' time, have a cure for 90% of cases.

The problem up to now

Hepatitis C is already curable in some patients. The definition of a cure is that, six months after therapy is stopped, viral load tests can find no trace of hepatitis C virus (HCV). This is called a sustained viral response (SVR).

Until now, therapy has consisted of weekly injections of a long-lasting 'pegylated' formulation of interferon-alfa, a naturally occurring virus-fighting protein, which can be made artificially. This is combined with ribavirin, an antiviral drug.

Both drugs can have severe side-effects. Interferon causes aches and pains, chills, exhaustion and depression, which can be intense. Ribavirin causes potentially debilitating anaemia.

At most, two-thirds of patients are cured, after up to a year of therapy, and no more than half of those with genotype 1, the most common and aggressive form of HCV. Cure rates for co-infected patients are worse: about 40% generally and about 30% for genotype. If hepatitis C is diagnosed and treated early, over two-thirds even of the co-infected can expect a cure: but for many people whose hepatitis was not detected early, or whose first course of therapy fails, a cure is not possible.

The latest results: co-infected people

Perhaps of most interest is a co-infection study presented in February:[1] a small study – 59 people – that hasn't gone on long enough to assess SVR rates yet, but with promising interim results.

Patients with no prior experience of hepatitis C treatment took telaprevir or placebo plus pegylated interferon/ribavirin (I/R) for twelve weeks. After this they continue taking I/R for another 36 weeks.

The biggest stumbling block in treating co-infection has been interactions between HIV and hepatitis C drugs. Studies indicate that combining telaprevir with the HIV protease inhibitors darunavir, fosamprenavir and lopinavir will be problematic, as levels of both the PIs and telaprevir were halved. Because of this, the patients on HIV therapy had to be either on efavirenz or atazanavir, plus tenofovir and FTC.

After twelve weeks, the results were impressive: 68% of patients taking telaprevir had an undetectable hepatitis C viral load, compared with 14% on placebo.

The viral response rate at twelve weeks is a good guide to whether patients will achieve an SVR. One exciting aspect of the new treatments is that they work fast. After just four weeks of treatment, 70% of patients on telaprevir already had undetectable hepatitis C viral loads, compared with 5% on placebo. In mono-infection trials, this has meant that treatment could be reduced to 24 weeks.

While these results are encouraging, it will be important to learn more about the response rates in people who failed to clear hepatitis C with a previous course of pegylated interferon and ribavirin, who are likely to be among the first to be offered the new drugs.

Trials in people without HIV

Results from the trials for telaprevir and boceprevir are especially impressive in patients who have previously experienced a relapse of hepatitis C after an initial response. In the case of boceprevir, there was no difference in the SVR rate in treatment-experienced and treatment-naive patients.

In two trials – SPRINT (drug-naive patients)[2] and RESPOND (drug-experienced)[3] – 67% of boceprevir recipients achieved SVR, compared with 38% of treatment-naive patients on a placebo and 21% of the drug-experienced. All these patients had genotype 1.

With telaprevir, in the studies ADVANCE[4] and REALIZE,[5] 75% of drug-naive and 65% of drug-experienced patients with genotype 1 achieved SVR, compared with 44% and 17% on placebo.

Patients took 24 weeks of boceprevir (which could be extended to 48 weeks), but in telaprevir trials patients only took the drug for up to twelve weeks, and any treatment for 24 weeks.

However, in all these studies people who did not respond to prior treatment with

pegylated interferon and ribavirin had a lower likelihood of SVR when retreated with a combination including one of the new drugs.

In the boceprevir trials, patients took a 'lead-in' of four weeks of interferon/ribavirin, to bring down their hepatitis C viral load and minimise the chance of resistance to the new drugs developing.

Resistance has not been a big concern in hepatitis C treatment, because interferon and ribavirin don't work in a way that facilitates it. But the new drugs work much more like HIV drugs, and hepatitis C has a ferocious replication and mutation rate, so could develop resistance.

There is a particular concern that people who fail to respond to boceprevir or telaprevir will develop resistance to most of the other protease inhibitors now being developed to treat HCV, which could be an argument for what doctors call 'watchful waiting'. This means waiting until more is known about how best to use the new drugs, or until newer drugs come along, and only treating if hepatitis C is causing rapid liver damage.

Trials without interferon

There were several reports, at last October's American Association for the Study of Liver Disease (AASLD) meeting, of studies using two new drugs of two new classes, without interferon or ribavirin.

Bristol-Myers Squibb has combined a hepatitis C protease inhibitor (BMS650032) with a drug (BMS790052) that inhibits a component of HCV called NS5A, which HCV needs to replicate.[6] It compared patients on dual therapy alone to patients on dual therapy plus I/R. All patients had failed to respond to I/R therapy before.

The two-drug combination reduced hepatitis C viral load to undetectable within four weeks in a majority of patients, whether or not they were also on standard treatment: 60% became undetectable on I/R plus the new drugs and 64% on the new drugs alone. After this, however, the balance swung towards standard treatment. By week twelve, the percentage of patients undetectable in the dual therapy group had reduced to 45%, while in the dual therapy-plus I/R group it had gone up to 90%.

Results of a study of two Gilead drugs, a protease inhibitor (GS9256) and a polymerase inhibitor (GS9190), in drug-naive patients, showed that some might be able to take the two new drugs plus ribavirin, leaving out interferon.[7] The mean viral load decrease on the two new drugs plus ribavirin was ten times larger than on the two drugs alone, and adding interferon made it 50 times larger.

Lots more to come

This selection of results only scratches the surface. A large number of different classes of drugs are in development, including a new drug called alisporivir (Debio 025), a cyclophylline inhibitor – a completely new class with a high barrier to resistance.[8]

There are even hints of a vaccine. One therapeutic vaccine has effected a change in some people's genetic response to interferon,[9] which enabled them to use this drug for the first time, and another produced a modest but long-lasting reduction in hepatitis C viral load.[10]

The advice of many doctors, for chronically infected patients who don't already have severe liver problems, has been to wait for new drugs – advice that the co-infected will need to consider for a few years yet.

Mark Nelson, HIV consultant at London's Chelsea and Westminster Hospital, comments: "I think next time one of my hepatitis C patients hears me say 'Hang on for the new drugs' they're going to hit me. I may have to keep on saying this for a while longer – but can now tell them that day is nearer."

The bad news, however, is the cost. The price set by Vertex, the company pegging its hopes on telaprevir, is rumoured to be £18,000 for 24 weeks' treatment. Add £10,000 for interferon and ribavirin and treatment becomes an expensive proposition.

A UK liver specialist, Professor Mark Thursz, of Imperial College, has said that if the drugs are priced at this level in the UK, their use may be restricted to people who have failed to respond to the current standard of care.

So, while we are getting closer to a more effective and tolerable cure for hepatitis C, we haven't quite got there yet. ■

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testing... testing... one, two, three [page eight]

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News from CROI [page twelve]

Patients have cells 'HIV proofed' in first step to a cure

1 Lalezari J et al. *Successful and persistent engraftment of ZFN-M-R5-D autologous CD4 T Cells (SB-728-T) in aviremic HIV-infected subjects on HAART.* 18th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, abstract 46, 2011.

Abacavir works less well in patients with low CD4 counts

1 Grant P et al. *Association of Baseline Viral Load, CD4 Count, and Week 4 Virologic Response with Virologic Failure in ACTG Study A5202.* 18th CROI, abstract 535, 2011.

New drug targets first step in infection

1 Nettles R et al. *Pharmacodynamics, safety, and pharmacokinetics of BMS-663068: a potentially first-in-class oral HIV attachment inhibitor.* 18th CROI, abstract 49, 2011.

Does diagnosis change risk behaviour? Studies disagree

1 Vallabhaneni S et al. *Seroadaptive tactics adopted by HIV-positive MSM can contribute to profound and sustained reductions in HIV transmission risk following HIV diagnosis.* 18th CROI, abstract 1038, 2011.

2 Heijman RLJ et al. *Changes in sexual behaviour after HIV diagnosis among MSM who seroconverted before and after the introduction of ART.* 18th CROI, abstract 1034, 2011.

we're getting there: towards a comprehensive hepatitis c cure [page fourteen]

1 Sulkowski M et al. *Interim analysis of a phase 2a double-blind study of TVR in combination with pegIFNα2a and RBV in HIV/HCV co-infected patients.* 18th Conference on Retroviruses and Opportunistic Infections (CROI), Boston, abstract 146LB, 2011.

2 Sulkowski M et al. *BOC combined with P/R for treatment-naive patients with HCV genotype-1: SPRINT-2 final results.* 18th CROI, Boston, abstract 115, 2011.

3 Gordon S et al. *HCV RESPOND-2 final results: high sustained virologic response among genotype-1 previous non-responders and relapsers to pegIFN/RBV when re-treated with BOC + Pegintron/RBV.* 18th CROI, abstract 116, 2011.

4 Jacobson IM et al. *Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naive patients: final results of phase 3 ADVANCE study.* 61st AASLD Conference, Boston, abstract 211, 2010.

5 Zeuzem S et al. *REALIZE Trial Final Results: Telaprevir-Based Regimen in Genotype 1 Hepatitis C Virus Infection in Patients with Prior Null Response, Partial Response or Relapse to Peginterferon/Ribavirin.* 46th Annual Meeting of the European Association for the Study of the Liver (EASL), Berlin, abstract 2371, 2011.

6 Lok A et al. *Combination therapy with BMS-790053 and BMS-650032 alone or with pegylated interferon and ribavirin (pegIFN/RBV) results in undetectable HCV RNA through 12 weeks of therapy in HCV genotype 1 null responders.* 61st AASLD conference, Boston, abstract LB-8, 2010.

7 Zeuzem S et al. *Dual, triple and quadruple combination treatment with a protease inhibitor (GS-9256) and a polymerase inhibitor (GS-9190) alone and in combination with ribavirin (RBV) or pegFN/RBV for up to 28 days in treatment naive, genotype 1 HCV subjects.* 61st AASLD conference, Boston, abstract LB-1, 2010.

8 Siddall R`*Fantastic' data on Novartis' first-in-class hep C antiviral.* Novartis press release, 1 April 2011.

9 Pockros PC et al. *GI-5005 therapeutic vaccine plus pegIFN/ribavirin improved sustained virologic response versus pegIFN/ribavirin in prior non-responders with genotype 1 chronic HCV infection.* 61st AASLD conference, Boston, abstract LB-6, 2010.

10 Klade CS et al. *Significant continuous viral load decline in treatment-naïve HCV genotype 1 patients after therapeutic peptide vaccination with IC41.* 60th AASLD conference, Boston, abstract 1558, 2009.

Increasing TB/HIV awareness: working with the third sector

THE TRUTH ABOUT TB

A worrying new chapter has opened in the fight against HIV, linked to the surge in tuberculosis (TB) cases in the UK. The close relationship between the two illnesses means people living with HIV (PLHIV) are at an increased risk of contracting TB. TB is also harder to diagnose in HIV positive people, it progresses faster and it is more likely to be fatal if undiagnosed or left untreated. With over 9000 new TB cases in 2009 in the UK – more than there were of HIV – this is an increasingly urgent issue.

It is critical that PLHIV understand the risks, and the need for early diagnosis and treatment. However, a lack of awareness about TB and stigma associated with both illnesses often delays or discourages affected people from seeking help.

This is why TB Alert has joined with the African Health Policy Network (AHPN) to raise awareness about TB and TB/HIV co-infection, particularly in the UK's African community which is disproportionately affected by the two illnesses.

A new leaflet has been launched as part of this work, developed with support from NAM. The leaflet explains what TB is, how it is transmitted, risk factors, common symptoms and the relationship between TB and HIV. The leaflet also advises people what action they should take if they are concerned about TB or HIV, and provides a comprehensive list of sources of advice and information.

The leaflet is just one of the free resources available as part of TB Alert's *The Truth About TB* programme, which brings together primary care trusts (PCTs), local authorities and the third sector to raise awareness about TB among the most vulnerable communities. To find out more and to order resources visit: **www.thetruthabouttb.org**.

About TB

TB is caused by bacteria transmitted through the air when someone with TB in the lungs or throat coughs or sneezes (although you have to be in close contact with someone with this form of TB for many hours to be at risk). TB can affect any part of the body. Symptoms depend on which part of the body is affected, but the most common are: a cough lasting more than three weeks; unexplained weight loss; loss of appetite; fever; night sweats; and extreme tiredness.

Anyone experiencing these symptoms should visit a doctor. TB is curable through a course of antibiotics and all treatment is free.

thanks to our funders

NAM's treatments information for people living with HIV is provided free thanks to the generosity of:

Abbott Laboratories Ltd; Abbott Fund; Allan & Nesta Ferguson Charitable Trust; Avexa Ltd; Boehringer Ingelheim Ltd; Bristol-Myers Squibb Pharmaceuticals Ltd; Cavidi AB; Delphic Diagnostics Ltd; Derek Butler Trust; Government of the United Kingdom, Department of Health; Government of the United Kingdom, Department for International Development; Diana, Princess of Wales Memorial Fund; Elton John AIDS Foundation; Estate of Sidney Klieff; F. Hoffmann-La Roche Ltd; Gilead Sciences Ltd; GlaxoSmithKline PLC; GlaxoSmithKline's Positive Action; Hugh Fraser Foundation; Lloyds TSB Foundation for Northern Ireland; Manchester City Council; Merck & Co., Inc; Merck Sharp & Dohme Ltd; Merck Sharp & Dohme Romania SRL; Miss Agnes Hunter's Charitable Trust; NHS Ashton, Leigh & Wigan; NHS Birmingham East and North; NHS Bolton; NHS Brighton & Hove; NHS Manchester; NHS Norfolk; NHS Pan-London HIV Prevention Programme; NHS Salford; NHS South East Essex; NHS South West Essex; NHS West Sussex; NHS Worcestershire Health Services; Pfizer Ltd; Plumptons Ltd; Roche Molecular Systems, Inc.; Roche Products Ltd; Sanofi Pasteur MSD; Schering-Plough Corporation; Janssen; UNAIDS; World Health Organization.

NAM would also like to acknowledge the generous support of its individual donors.

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Every year NAM provides information resources, like *hiv treatment update*, to thousands of people living with HIV, completely free of charge. To do this we really do rely on the generosity of people like you to help us continue our vital work. You can make a difference today. Please make a donation by visiting **www.aidsmap.com/donate** or by ringing us on **020 7840 0050**.

where to find out more about hiv

- **Find out more about HIV treatment:**
  NAM's factsheets, booklets, directories and website keep you up to date about key topics, and are designed to help you make your healthcare and HIV treatment decisions. Contact NAM to find out more and order your copies.
- **www.aidsmap.com**
  Visit our website for the latest news about HIV & AIDS, a fully searchable treatments database and a complete list of sexual health clinics in the UK.
- **THT Direct**
  Offers information and advice to anyone infected, affected or concerned about issues relating to HIV and sexual health.
  0845 1221 200
  Mon-Fri, 10am-10pm Sat-Sun, 12pm-6pm
- **i-Base Treatment Phoneline**
  An HIV treatment phoneline, where you can discuss your issues with a treatment advocate.
  0808 8006 013
  Mon-Wed, 12pm-4pm