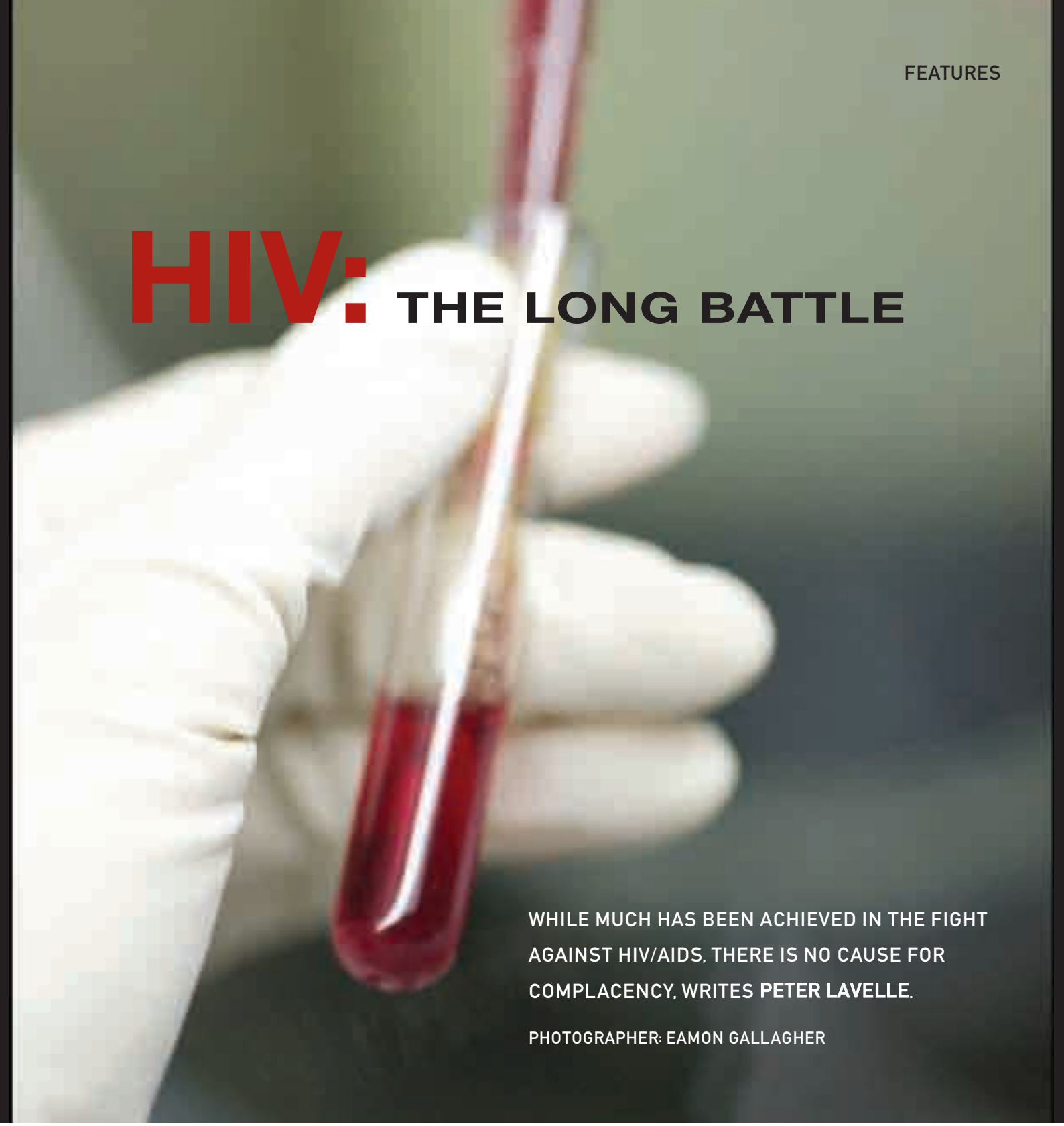

HIV: THE LONG BATTLE

WHILE MUCH HAS BEEN ACHIEVED IN THE FIGHT AGAINST HIV/AIDS, THERE IS NO CAUSE FOR COMPLACENCY, WRITES **PETER LAVELLE.**

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Since it first appeared in the early 1980s, HIV/AIDS in the developed world has gone from being a death sentence to a chronic but manageable condition – with life-saving antiviral drugs, an infected person can live a normal lifespan.

In the developing world, it's a different story. Of the 40 million cases worldwide, about 30 million are in Sub-Saharan Africa and six million in South and South-East Asia. The great majority of these sufferers do not have access to the drugs they need.

But there is no cause for complacency in Western countries such as Australia either, as HIV continually mutates into drug resistant forms. And over the past few years, an increase in unprotected sex has given rise to more HIV cases.

A type of virus known as a retrovirus, Human Immunodeficiency Virus attacks key immune system cells. Once it enters a person's bloodstream, it invades the lymph nodes and targets white blood cells called T lymphocytes and macrophages.

It binds to specific receptor molecules on the surfaces of these cells (two such receptors are called CD4 and CCR5) then enters the cells. Once inside, it uses an enzyme called reverse transcriptase to convert its RNA into DNA, which is then incorporated into the host cell's genes.

This "rogue" DNA uses the cell's protein-making machinery to make millions of copies of itself that are released into the

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Dr Nick Medland, a GP and director of the Victorian AIDS Council Gay Men's Health Centre Clinics

bloodstream to infect other white blood cells. In the process, the white cells' functioning is impaired, they are destroyed and their numbers fall.

In developed countries, HIV transmission most commonly occurs during unprotected sex between men (whereas heterosexual transmission is common in developing countries). The other common form of transmission is via blood in a contaminated needle shared between drug users.

Transmission from patients to health-care workers (or vice-versa) via needle-stick injury, for example, is possible, but rare. Pregnant women with the infection can pass it to the foetus, or to the baby during breastfeeding. There is no evidence that HIV is spread by saliva or casual contact.

When people are first exposed to HIV, the initial symptoms, if any, are slight and resemble a mild flu within a month or two of exposure. They may have a fever, headache, feel tired and have enlarged lymph nodes in the neck and groin. These symptoms usually go after a few weeks. In other cases, there are no symptoms of an initial illness at all.

Characteristically, there is a long lag before anything else happens – the person may stay well for many years. This is because although the virus is attacking the immune system, the body is still able to mount a response against it that slows its progress.

Gradually though, HIV depletes T cells to the point where the immune system is so damaged it is no longer effective. The person may start to get mild infections such as oral or vaginal thrush or shingles. They lose weight, get tired frequently, develop sweats – especially at night – and suffer from diarrhoea. The lymph nodes in the groin and neck become (and stay) enlarged.

When the level of T cells becomes critically low, people start to get serious opportunistic infections, ones that probably wouldn't be occurring if HIV were not ravaging the immune system. These can include pneumocystis pneumonia, meningitis, encephalitis and severe fungal and viral infections.

Sufferers can also develop other serious conditions of the brain and nervous system and cancers such as lymphomas and Kaposi's sarcoma – round brown, reddish or purple spots that develop on the skin or in the mouth. This stage is known as AIDS.

But the progression from contracting HIV to AIDS is quite variable – rarely, some people get full-blown AIDS a few months after exposure while others stay well for 20 years. Most people stay well for eight to 10 years before getting any sign of AIDS. Some go through periods of illness followed by recovery only to become ill

again. For reasons that aren't understood, a small number never get symptoms at all.

Professor Sharon Lewin, president of the Australasian Society for HIV Medicine and director of the Infectious Diseases Unit at The Alfred Hospital in Melbourne, says the situations in which people seek testing for HIV/AIDS vary. Those aware they are in a high-risk group may have regular screening (sexually active homosexual men, for example, should have a yearly HIV test).

However, a significant number of new diagnoses of HIV infection are made when someone already with full-blown AIDS goes to a doctor – these are often people who may not have known they were at risk of HIV infection or may have suspected they had been exposed but delayed seeking medical help, Professor Lewin says.

The screening test for HIV looks for antibodies to HIV in the blood. Dr Roger Garsia senior immunopathologist at the Royal Prince Alfred Hospital in Sydney and Chair of the RCPA Immunopathology Advisory Committee says there's a whole range of licensed screening tests which work by detecting antibody to HIV.

Traditionally, clinicians used the ELISA test as a screening test, with another test, the Western Blot to confirm the diagnosis. The ELISA test is an enzyme-linked immunoassay technique, which is very sensitive – it gives few false negatives but it does have the problem of a significant amount of false positives, he says. So a positive ELISA test must be followed by a Western Blot, which detects antibodies to specific HIV proteins and is able to confirm the diagnosis.

In recent years though, the ELISA screening test has been superseded in some labs by combination screening tests, which both test for antibodies and the presence of viral proteins simultaneously (these are known as antigen – antibody combination assays). The combination screening test still needs to be confirmed by a positive Western Blot, says Dr Garsia.

However, there is a window period following infection in which the body hasn't yet manufactured enough antibodies for the tests to be positive. This period is about 3-4 weeks, but can be as long as 3 months. So a person who tests negative within this period may need a subsequent test if HIV infection is strongly suspected on clinical grounds. "Most people will test positive within 6 weeks after they've been infected," says Dr Garsia.

A person with HIV probably won't need treatment in the early stages of the condition. Dr Nick Medland, a GP and director of the Victorian AIDS Council Gay Men's Health Centre Clinics, says treatment is best left as long as possible. That's because antiviral drugs, the mainstay of treatment, are associated with side effects and serious toxicity in some cases, he says.

"Now with HIV, you need 95 per cent adherence to medication or you get treatment failure. And that leads to resistance to HIV drugs and it's harder to treat them." So treatment is withheld until it looks like the HIV has progressed to an advanced stage, he says.

The point at which someone is treated depends on whether they have symptoms, their T-cell count (more commonly known as the CD4 count) and to some extent their viral load (the amount of virus present). A healthy, uninfected person usually has 800 to 1,200 CD4 cells per cubic millimetre of blood. Usually someone with HIV isn't treated until their CD4 count falls below 200 cells per mm3.

Says Professor Lewin: "Below this amount, we recommend treatment because the risk of progressing to AIDS is quite significant. In someone with a CD4 count greater than 350, we don't recommend treatment because their risk of progression is quite low, and the risks of toxicity and resistance to the drugs outweigh the risk of disease progression." Instead, a person with a CD4 count of 350 or more would be monitored with a blood test every three months or so, she says.

Between 200 and 350, the decision to treat is controversial. Some clinicians recommend treatment, others don't; Australasian Society for HIV Medicine recommendations are that a person is not treated but is monitored closely. If their CD4 count starts to fall rapidly towards 200, treatment may be started. Or if their count is between 200 and 350 and they have a high viral load – more than 100,000 copies per millilitre of blood, meaning

Professor Sharon Lewin, president of the Australasian Society for HIV Medicine and director of the Infectious Diseases Unit at The Alfred Hospital in Melbourne

there is a possibility their CD4 count could fall quickly – they too may be treated.

If someone has a count greater than 200 and has symptoms such as fever, rash, diahorrea, Kaposi's sarcoma or immune-related conditions associated with HIV, these people should be treated as such conditions tend to improve with antiviral drugs, Professor Lewin says.

Such drugs work by inhibiting HIV replication – and this can be measured by a fall in the viral load. The aim is to get the viral load to undetectable levels – defined as being fewer than 50 copies per millilitre. Most people reach this level one month after commencement of treatment, says Professor Lewin.

If they do not get undetectable levels of virus by three months, that would be considered a treatment failure, which could be due to drug resistance, poor adherence, or failure to absorb or metabolise the drugs.

"CD4 counts are not used as an initial measure of treatment success because there are many other factors that influence the return of T cells, not just the antiviral treatment," Professor Lewin says. "For example, T cells return more slowly in older patients or with different kinds of virus strains."

There are three groups of HIV antivirals. They all work by interrupting the reproductive cycle of the virus. Nucleoside analogue reverse transcriptase inhibitors (NRTIs) inhibit the enzyme that allows RNA to manufacture DNA, a critical step for the virus.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) also work this way but have a different chemical structure. A third class of anti-HIV drugs, called protease inhibitors, interrupts virus replication at a later step in its life cycle.

Society for HIV Medicine treatment guidelines recommend the use of at least three anti-HIV drugs, in general using two NRTIs and one drug from a different class, either a NNRTI or a protease inhibitor.

The choice within a class is made on the basis of how potent the drug is, its side effects and whether the virus has an existing resistance to that drug. Adherence to the treatment, and regular monitoring of viral loads and CD4 levels, is vital.

"Clinical trials show that people with HIV who take an antiviral combination for the first time, and adhere to it, have a greater than 90 per cent success rate. Those people remain well, probably indefinitely," Dr Medland says

Sticking with the regimen has become easier for patients as the drugs have become less toxic and combination tablets have become available. Many patients are on just two or three tablets a day.

But side effects such as lipid abnormalities, diabetes and liver toxicity remain a problem, though more so with the older drugs, says Dr Nick Medland. The prognosis is good if a person keeps taking the drugs as instructed.

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There is a large amount of research into vaccines – both prophylactic (designed to prevent HIV transmission) and therapeutic (designed to counter the effects of the condition). Some are being trialled already. There have been promising results in animal studies, but there are no prospects of an effective vaccine for humans for at least five to 10 years, says Professor Lewin.

Hence the importance of public health campaigns. Over the past five years there has been an increase in the number of new reported HIV cases in Australia, probably because of a rise in unprotected sex in high-risk groups, and a rise in sexually transmitted infections, which make transmission more likely, says Dr Medland. So these public health campaigns remain as important as ever.

GPs NOTE: This article is available for patients at http://pathway.rcpa.edu.au