ANTI-HIV DRUGS

Scientists have been striving to develop effective drugs against the human immunodeficiency virus (HIV) since it was identified as the causative agent of AIDS in the 1980s. For the first time since the epidemic emerged, clinicians now have several different classes of anti-HIV drugs at their disposal, and are using them in combination to develop effective treatments for HIV/AIDS.

This briefing outlines recent developments in anti-HIV drugs, and examines the issues that arise.

ANTI-HIV DRUG TARGETS

HIV is a retrovirus, with a simple structure described in **Box 1**, and illustrated **in Figure 1**. It contains genes coding for a number of unique viral enzymes, required at different stages of the virus's life cycle (see **Box 2** and **Figure 2**). One of these is reverse transcriptase, required to make copies of the viral genes once it has infected human cells. Another is HIV protease, which is needed at the end of the viral life-cycle to 'snip' viral proteins down to size for packaging into new HIV particles. All the antiretroviral drugs licensed for use against HIV infection to date (see **Table 1**) target one of these two HIV enzymes.

Reverse Transcriptase Inhibitors (RTIs)

HIV's reverse transcriptase enzyme makes DNA copies of viral RNA by linking together the basic building blocks of DNA (nucleotides containing the bases A, C, G and T - the four bases of the genetic code) into long chains. The first anti-HIV drugs (the nucleoside analogues or NAs) were analogues of these basic DNA building blocks, modified to prevent them from linking into chains. They 'look' sufficiently like the nucleotide subunits to be taken up by the enzyme, but their inability to link to the next base in the sequence means that the DNA chain is terminated and copying inhibited. Five NAs have been licensed for use in the US and Europe (Table 1) - two (AZT and D4T) are derivatives of thymidine (the T in the genetic code), two (ddC and 3TC) of cytidine (C) and one (ddI) of inosine (a close relative of guanosine, G). In addition to these, at least one other NA (abacavir) is being tested in clinical trials.

More recently, researchers have developed a second class of RTIs, the non-nucleoside reverse transcriptase inhibitors (NNRTIs). These drugs also inhibit reverse transcriptase, but do so by binding directly to the enzyme itself rather than mimicking the building blocks it uses. They are designed to bind to the enzyme's active site (which normally 'picks up' DNA building blocks for insertion into the new chain). Two NNRTIs have been licensed for use in the US to date (Table 1), delavirdine and nevirapine (also licensed in Europe), although more are being assessed in clinical trials (e.g. efavirenz).

BOX 1 HIV STRUCTURE

HIV is a **retrovirus**, which means that its genes are coded in RNA (a nucleic acid closely related to DNA) rather than DNA. It consists of two single strands of RNA surrounded by various proteins, contained within a spherical fatty (lipid) envelope (**Figure 1**) around 10nm in diameter (a nm is $1/1000^{th}$ of a mm). Each RNA strand contains a copy of each of the virus's 9 genes, which encode the various proteins needed to infiltrate the host cell, integrate itself into the host genome, and replicate, assemble and release new virus particles. These include the core protein that surround the RNA strands, matrix protein that lines the inner surface of the lipid envelope, glycoproteins that straddle the membrane (gp41) and protrude from its surface (gp120) and enzymes such as reverse transcriptase and HIV protease.
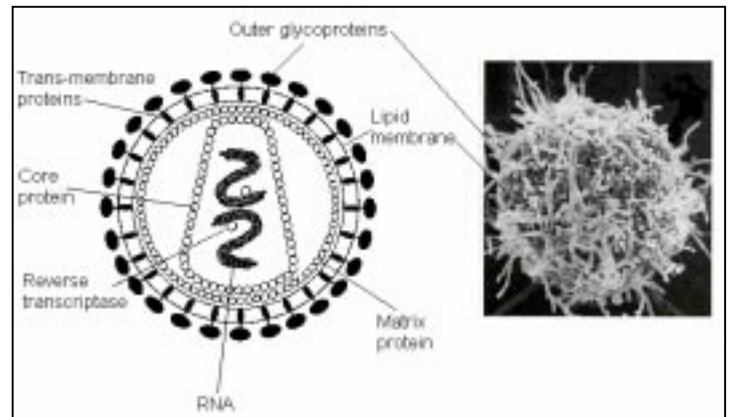
FIGURE 1 MAIN COMPONENTS OF HIV

TABLE 1 SUMMARY OF LICENSED ANTI-HIV DRUGS

Name	Type	Typical dose	Potential side-effects
3TC	NA	2 x 1 pill per day	Headache, fatigue
AZT	NA	2 x 1 pill per day	Nausea, headache, insomnia, anaemia
ddC	NA	3 x 1 pill per day	peripheral neuropathy (PN), mouth ulcers
ddI	NA	2 x 2 pills per day (on empty stomach)	Nausea, diarrhoea, PN, pancreatitis
D4T	NA	2 x 1 pill per day	Nausea, headache, PN, diarrhoea
delavirdine	NNRTI	3 x 4 pills per day (with water)	Rash, headache, abnormal liver function
nevirapine	NNRTI	2 x 1 pill per day	Rash, abnormal liver function
indinavir	PI	3 x 2 pills per day (on empty stomach, or with low fat snack)	Kidney stones, nausea, abnormal distribution of fat, high blood fat, glucose intolerance
nelfinavir	PI	3 x 3 pills per day (with food)	diarrhoea, abnormal distribution of fat, high blood fat, glucose intolerance
ritonavir	PI	2 x 6 pills per day (with food)	Nausea, vomiting, diarrhoea, weakness, abnormal distribution of fat, high blood fat, glucose intolerance
saquinavir	PI	3 x 6 pills per day	Nausea, diarrhoea, headache, abnormal distribution of fat, high blood fat, glucose intolerance

BOX 2 HIV LIFE-CYCLE

Like all viruses, HIV is not capable of independent replication - it can only make new viruses by infecting human host cells. Among the main stages in HIV's life-cycle (depicted in **Figure 2) are:**
- attachment of HIV to the outer surface of the human host cell, followed by entry of the virus into the cell;
- manufacture of DNA copies of HIV's (RNA) genes, and incorporation of these copies into the cell's genes;
- hijacking of the cell's DNA reading and protein manufacturing systems to make new (RNA) virus genes and the long chains of viral proteins coded for by the HIV genes;
- transport of these various components to the cell membrane, where the long chains of proteins are cleaved into smaller pieces (by HIV protease enzyme) and the new HIV particles are assembled and released.

Among HIV's known targets are helper T cells (called CD4+T cells which co-ordinate immune responses and act as the immune system's memory cells). These contain surface receptors known as cluster designation 4 (CD4) which bind tightly to the HIV gp120 proteins (Figure 2). However, there is increasing evidence that HIV also infects other immune cells including T cells that lack CD4, B (antibody producing) cells and CD4+ macrophages. After binding, the viral and host cell membranes fuse and the HIV (RNA) genes, proteins and enzymes enter the infected cell.

Once inside the cell, the virus's immediate priority is to protect its genes from attack. At this stage, the viral genes are RNA sequences, a form of nucleic acid that is normally used by cells to make temporary copies of genes (for making proteins) and which is then rapidly broken down. In order to protect its genes from attack, the virus uses its reverse transcriptase enzyme to make (DNA) 'hard copies' of its RNA gene sequences (Figure 2). These DNA copies are then spliced into the host cell's genes with the aid of other viral enzymes. This reverse transcription process is one of the stages in HIV's life-cycle that is unique to the virus (host cells do not normally contain reverse transcriptase) and is thus one of the key targets for anti-HIV drugs. Having integrated DNA copies of its genes into the host genome, the 'provirus' is now safe from attack, and may remain dormant within the host cell. At some point in the future the HIV genes are transcribed back into RNA by the host cell, and these sequences can then be:
- translated into regulatory proteins by the cell's machinery (it is these viral proteins that hijack the cell, turning it into a factory for producing HIV particles);
- translated into long chains of core proteins and enzymes (these are not functional until they are cleaved into their component parts by an HIV protease enzyme as part of the final maturation process);
- packaged as RNA genes into the new virus particles.

The various HIV components are assembled into new virus particles that bud out from the host cell's membrane. As noted above, these immature viruses are not infectious until the long chains of viral core proteins are cleaved by HIV protease. Since this enzyme is unique to HIV, this step is another key target for anti-HIV drugs (protease inhibitors, see Figure 2).

In addition to the NAs and NNRTIs, another class of drugs are under development that act on reverse transcriptase. **Nucleotide analogues** work in exactly the same way as NAs, but unlike their close relatives do not have to be converted (phosporylated) to their biologically active form in the body. This means that they may stay active within the body for longer. Nucleotide analogues now being assessed in trials include adefovir dipivoxil and PMPA, although neither has yet been licensed.
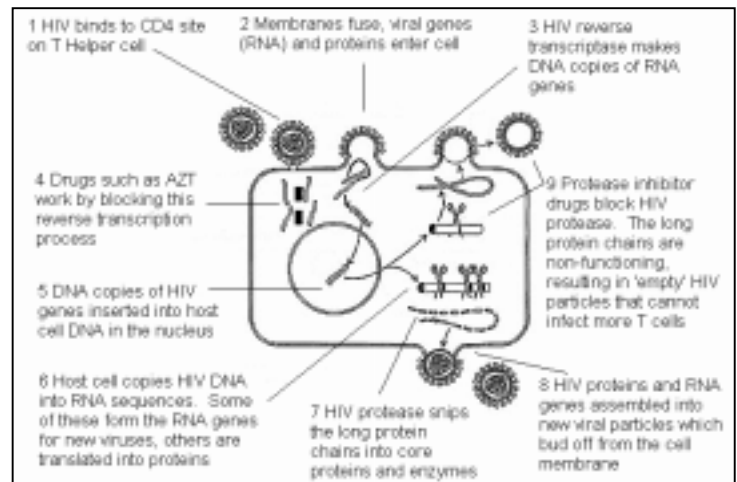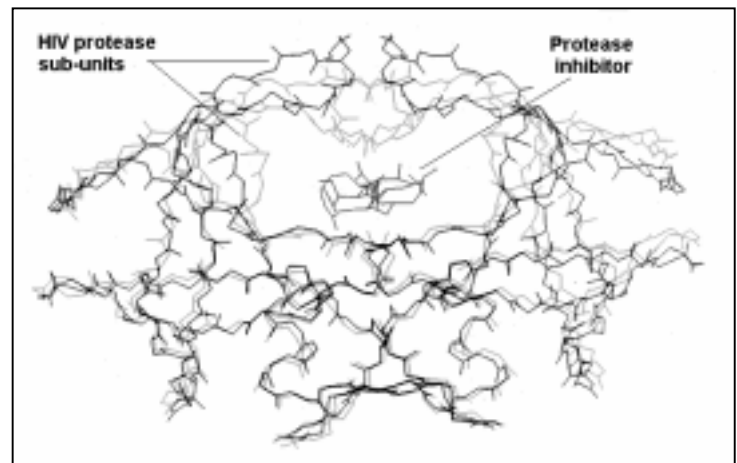
FIGURE 2 HIV LIFE CYCLE

FIGURE 3 INHIBITION OF HIV PROTEASE

PROTEASE INHIBITORS (PIs)

As outlined in Box 2 and Figure 2, HIV protease is involved in the later stages of the viral life cycle, producing the final versions of many of the proteins required to form an infectious new HIV particle. It consists of two identical protein sub-units, which 'slot together' leaving an active site in the middle (**Figure 3**). PIs are small molecules that are designed to fit snugly into this site (see Figure 3), inhibiting the enzyme.

Four PIs have been licensed for use in the US and Europe so far (Table 1) - saquinavir, ritonavir, indinavir and nelfinavir. Of these saquinavir is available in two formulations, invirase (a hard gel which is only poorly absorbed) and fortovase (a soft gel which is more fully absorbed). Several more are expected soon, with new PIs (e.g. amprenavir) presently being tested in clinical trials.

Other Targets

New drugs are also being developed against other targets. As detailed in **Box 3**, these include drugs to prevent viral attachment to human cells, agents that target other HIV (e.g. regulatory) genes and enzymes (e.g.

BOX 3 OTHER HIV TARGETS

Drugs that Prevent Viral Binding
HIV uses the viral proteins (gp120 and gp41) on its outer surface to bind to receptors (usually CD4) and co-receptors (called chemokine receptors) on the human cells it infects. Various approaches have been tried to develop drugs that block these sites, or interfere with their structure in some way. For instance, a gp41 blocking agent called T-20 has been developed and is being tested in humans in the US, while several agents that block the main co-receptors bound by HIV are currently under investigation.

Drugs that Target HIV Regulatory Proteins
HIV has a number of genes (*tat*, *gag*, *rev*, *vpr*, *nef*, *vpu* and *vif*) that code for regulatory proteins controlling various aspects (e.g. timing, speed) of viral replication, and these are also targets for anti-HIV drug research. To date, few inhibitors of these regulatory proteins have been identified (a tat inhibitor was developed but proved ineffective in clinical studies), although research on the exact structure and function of the proteins continues.

Other Approaches
Other potential targets for anti-HIV drug research include:
- **RRIs** (ribonucleotide reductase inhibitors) act on a human enzyme (ribonucleotide reductase) used to manufacture the basic nucleic acid building blocks. One such drug, hydroxyurea, has been shown to enhance the action of certain NAs by increasing the rate at which HIV incorporates them into DNA. Serious side effects (inhibiting red blood cell production in bone marrow) mean that people taking this drug to boost the effectiveness of NAs need careful monitoring.
- HIV zinc finger inhibitors (drugs which inhibit part - the so called 'zinc finger' - of the HIV core protein, thought to be involved with binding and packaging HIV genes into new virus particles).
- HIV integrase inhibitors (drugs which inhibit HIV's integrase enzyme, which integrates the viral DNA into the host cell DNA).
- Anti-sense probes - short pieces of nucleic acid that are designed to specifically bind to (and thus block) HIV's genes.

FIGURE 4 PROGNOSTIC VALUE OF BIOLOGICAL MARKERS

integrase) as well as drugs such as hydroxyurea which act on a human enzyme to enhance NA activity. Several of these drugs are available through clinical trials although none have yet been fully licensed as anti-HIV treatments.
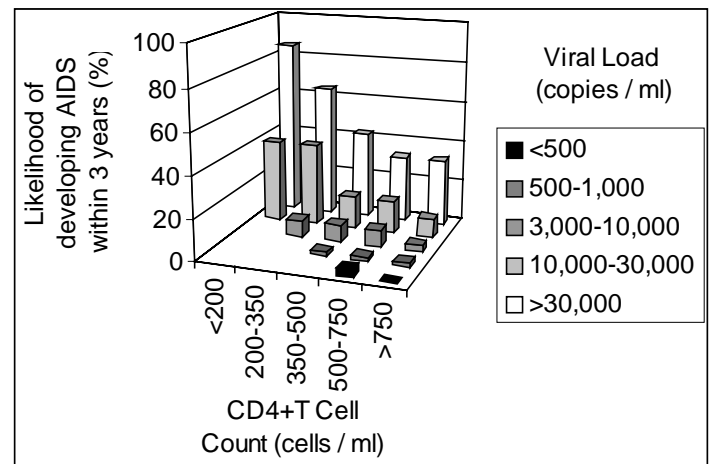
PRINCIPLES OF ANTI-HIV TREATMENT

Clinical thinking on who should receive what type of treatment and when has evolved over the years, with the availability of the new drugs, informed by increasing experience from clinical trials and aided by the development of new (e.g. viral load) tests. Decisions when to start or change treatment, which drugs to use, etc., are a matter for the patient and their doctor, guided by consensus guidelines published by expert panels (e.g. the British HIV Association; BHIVA). The principles behind current guidelines are outlined below.

Biological Markers

Two **biological markers** are commonly used to guide and assess anti-HIV treatments (**Box 4**). First is the **CD4+T cell count**, which is the level of these cells in the blood and is taken as a measure of the extent to which HIV has already damaged the immune system. Second, is the **viral load**, measured by the number of HIV genes

detectable in the blood, which is taken as a guide to the virus's replication rate. The relationship between CD4+T cell counts, viral load and disease progression is illustrated in **Figure 4**, which shows the proportion of subjects in a multi-centre AIDS cohort study in the US progressing to AIDS within 3 years. Nearly 86% of the men in the study with the lowest baseline (see below) CD4+T cell counts (<200 cells/ml) and highest viral loads (>30,000 copies/ml) developed AIDS within the first three years of the study. In contrast, none of those with the highest cell counts (>750 cells/ml) and lowest viral loads (<500 copies/ml) progressed to AIDS within this time.

The value of such markers as diagnostic tools and as a means of monitoring effectiveness of treatment is widely accepted, and guidelines recommend levels of both should be measured before starting anti-HIV treatment to establish an accurate **baseline**. Once baseline levels have been established, doctors can monitor the effectiveness of a chosen treatment by conducting further tests at regular intervals. The most potent anti-HIV drug combinations in current use (see later) can have dramatic effects, reducing viral load to 1/100th of baseline levels within 2 weeks.

Drug Resistance

Anti-HIV drugs (NAs) were initially tested and used as **monotherapies** (i.e. given to patients as single drugs rather than in combination with other drugs). Trials in the mid-1980s showed that AZT (the first NA licensed) resulted in clinical benefits (improvements in survival, fewer opportunistic infections) and a rise in CD4+T cell counts when given to people with AIDS. But subsequent research showed that these effects were often transient, and it became apparent that HIV was developing resistance to the drug when viable AZT-resistant strains of the virus were isolated from patients receiving the drug. It has since emerged that the problem of drug

BOX 4 CD4+T CELL COUNTS AND VIRAL LOAD TESTS

CD4+T Tests
CD4+T cells (the immune system's T helper cells that contain CD4 receptors) are among the cells most commonly infected by HIV. CD4+T cell levels in blood vary considerably (depending on the time of day the blood sample is taken, fatigue, etc.) but are normally within the range 500-1,600 cells/ml, and comprise some 20-40% of total white blood cells. Levels of these cells decline drastically in people infected with HIV, and the extent of this decrease is accepted as a measure of the damage done to the immune system by the virus. Doctors often start anti-HIV therapy when CD4+T cells fall below 500 cells/ml (or when they account for less than 15% of all white blood cells), and prescribe drugs to prevent opportunistic infections at levels below 200 cells/ml.

Viral Load Tests
Viral load tests measure the amount of HIV RNA present in the blood, and are thus used as a yardstick to gauge the extent of viral replication. Three different types of tests are available:
- bDNA (branched DNA) test.
- RT-PCR (reverse transcriptase polymerase chain reaction).
- NASBA (nucleic acid sequence based amplification).

Each of these tests can give different results - for instance, HIV RNA values obtained by RT-PCR are roughly twice those obtained using bDNA. Even within a single type of test, duplicate samples can give results varying by up to threefold. Tests typically in use in laboratories currently measure down to ~500 copies/ml, although the most recent tests can detect down to 25 copies/ml. Doctors may start treatment with anti-HIV drugs when viral loads exceed a threshold of ~10,000 copies/ml.

BOX 5 DRUG RESISTANCE AND HIV

HIV mutation and selection
When genes are replicated in human cells, complex 'proof reading' mechanisms ensure that the copies are faithful reproductions of the originals. HIV has no such systems, so any random changes in the sequence (mutations) made by HIV's reverse transcriptase (used to copy HIV genes) remain uncorrected, and are translated into mutant versions of the viral proteins. Very small changes in protein sequence can have very big effects on their function. Most of the mutations will thus result in non-viable viruses, but an occasional mutation will confer an advantage to the virus (e.g. drug resistance) in its current circumstance (e.g. exposure to the drug). The resistant strain will be 'selected' by the continued presence of the drug, and will eventually predominate.

HIV genes involved
Mutations in the genes coding for reverse transcriptase (affecting the site where the enzyme binds DNA building blocks) can lead to strains resistant to NAs. Entirely different mutations in the same reverse transcriptase gene (affecting the site where these drugs bind to the enzyme) can cause resistance to NNRTIs. Resistance to PIs is caused by mutations in the HIV protease gene, and may require the accumulation of several mutations.

Cross-resistance
Mutations may confer resistance to more than one drug in a particular class (**cross-resistance**). This is a complex process, and can operate at different levels, with some mutations conferring resistance to just one drug within a class, others to more than one drug, and yet others to all drugs within a given class. Some mutation patterns (e.g. where the virus has accumulated several mutations) may lead to high level resistance. Overall, the profile of resistance acquired by an HIV strain will depend on the pattern of mutations it has accumulated. Gene sequencing (genotype) tests that detect resistance mutations have been developed but will only detect known mutations. Phenotype tests, which assess the overall capability of HIV to grow in the presence of different drug combinations, are possible but are currently very expensive. Single mutations cannot cause cross-resistance between classes of drugs (because different classes of drug act at different sites). However, an HIV strain may accumulate a series of mutations at the relevant sites and thus eventually acquire resistance to all the different classes of drugs it has been exposed to. The use of combinations of different drugs is designed to prevent this from happening, by effectively suppressing viral replication, thus denying HIV the opportunity to produce new mutations. So far there is no evidence of widespread resistance to multiple classes of drugs emerging in people receiving potent triple combination therapies. Some scientists believe that such multiple resistance is unlikely to develop because the number of mutations required would have a deleterious effect on the virus's capacity to replicate itself. While there must be a limit to the number of mutations that HIV can tolerate, this has yet to be determined.
Source: NAM HIV + AIDS Treatments Directory, 1998

resistance is not confined to AZT - the virus is able to develop resistance to each of the main anti-HIV drugs developed so far. As outlined in **Box 5**, this is because HIV has a built-in mechanism that guarantees a high mutation rate when it replicates itself. Once a resistant strain emerges, the continued presence of the drug will ensure that it becomes the predominant strain.

Another consideration affecting choice of treatment is the issue of **cross-resistance**. As explained in Box 5, patients who 'fail' drug therapy because of the emergence of resistant HIV may find their therapeutic options somewhat limited, since their virus may also be resistant to drugs they have not yet taken. For this reason, some doctors are extremely cautious about starting anti-HIV therapy at an early stage of infection. A person's previous exposure to anti-HIV drugs will thus influence the treatments they are likely to receive in the future (tests are being developed that type the resistance of HIV strains and allow the best treatment options to be selected).

Combination Therapy
Many researchers now believe that the development of drug-resistance was a key factor limiting the effectiveness of anti-HIV drugs in the past. Such thinking has had profound effects on the clinical use of these drugs in recent years. The biggest single effect has been a switch away from the use of monotherapy to the use of **combination therapy**, where two or more different drugs

are given simultaneously. The theory behind such a move is that:
- suppressing viral replication will prevent development of resistant (mutant) strains (because mutations occur only when the virus replicates - see Box 5);
- while individual viruses may develop resistance to one of the drugs used, they will still be susceptible to one or more of the others;
- if a virus does acquire all the mutations needed to resist all the drugs, such wholesale changes in its genes might 'weaken it', adversely affecting its ability to replicate, infect new cells, etc.

Results from clinical trials using combinations of anti-HIV drugs prove that two or three drugs taken together are more effective than one. For instance, two large clinical trials in 1995 showed that **dual combinations** of AZT + ddI or AZT + ddC were more effective than AZT alone in delaying the onset of AIDS and prolonging life in symptom-free people with HIV. More recent studies using **triple combinations** have given even more encouraging results, with combinations including a PI (i.e. 2 NAs + 1 PI) reducing viral load below detectable levels in some 70-80% of recipients. Two recent trials show that such combinations also have clinical benefits for patients, at least in the short-term. In one, AZT + 3TC + indinavir (a PI) delayed clinical events in people with advanced disease previously given AZT alone. In the other, AZT + 3TC + saquinavir (another PI) was shown to be more effective than dual therapy at preventing disease progression in previously untreated people.

Another approach is to use triple combinations involving an NNRTI and two NAs. Although there is little evidence concerning the clinical outcomes of such combinations, studies on biological markers look promising. In one such study, a combination of nevirapine (an NNRTI) + AZT + ddI (both NAs) led to a reduction of viral load to below detectable levels in 70% of the recipients. Tests conducted after 12 months of treatment with this combination failed to show the development of any nevirapine-resistant strains (none of the people in the trial had previous exposure to this drug), suggesting that suppressing HIV replication does indeed delay the emergence of drug resistance.

Current clinical guidelines thus favour the use of triple combinations of anti-HIV drugs, usually including a PI, although there is continued debate over what is the most effective combination and when to start using it (see later).

Aim of Combination Therapy

The current philosophy underpinning anti-HIV therapy is to reduce the viral load as much as possible for as long as possible. In practice the most potent anti-HIV combinations can reduce viral loads below detectable limits (~500 copies/ml for commonly used tests), within 12-16 weeks. Studies using more sensitive tests suggest that in many cases the viral load decreases below the current detection limit of 25-50 copies/ml although reduction to such levels may take longer to achieve.

On-going clinical trials suggest that current anti-HIV drug combinations can suppress replication to below detectable limits in most patients who are able and willing to take the drugs for up to 2 years, but the extent to which these effects translate into long-term clinical benefits is unknown. One drawback is that the tests show only what is happening in the blood - researchers already know that HIV has many other 'hiding places' within the body (lymph nodes, nervous system, etc.). Research has shown that up to 2 years suppression with anti-HIV drugs does not eradicate the virus - if treatment is stopped, there is a rapid rebound in replication, and a sharp rise in blood HIV levels.

Other Considerations

Choosing the most appropriate therapy involves people with HIV and their doctors weighing the clinical advantages of the available treatments against the disadvantages. These include multiple side-effects, the daunting nature of some drug regimes (which can involve up to 20 pills a day, some of which are taken in the middle of the night, others on a full stomach, others with water, etc.) and the fact that treatment may need to continue for years. Such factors mean that combination therapy has a major impact on everyday life, and that compliance with complex drug regimes is difficult. However, failure to adhere to a drug regime can lead to the emergence of drug-resistant strains, which may in turn limit future therapeutic options. It is thus important that doctors and patients consider such factors very carefully when selecting the most appropriate treatment and that patients get the support they need to help with any problems that might arise.

There are a number of other considerations that may also influence the choice of anti-HIV treatments. In the case of pregnant women, trials have shown that AZT reduces the risk of **maternal transmission** of HIV by around two-thirds if given during pregnancy. So far, only AZT has been proved to do this with no risk of birth defects or miscarriage. Research is currently underway to assess the safety and effectiveness of other anti-HIV drugs, and to determine the optimum timing for treatment. Treatment options for **children** are also more restricted, partly because fewer drugs are licensed for use in children and some of these are not available in the appropriate formulation (e.g. powders or liquids that children find easier to swallow than pills). Children also differ from adults in a number of important respects, in the way they metabolise and tolerate the drugs, the fact that their immune systems are not fully developed, etc.

ISSUES

Guidelines on the use of anti-HIV drugs have been published by expert panels such as the International AIDS Society (IAS), US Public Health Service (USPHS), British HIV Association (BHIVA) and (UK) National Association of Providers of AIDS Care and Treatment (PACT). However, a number of fundamental questions remain unanswered. Doctors and patients still do not know which is the most effective combination of drugs, or when best to start treatment. Nor do they know

whether current treatments will eventually eradicate the virus, or merely suppress replication for a long time (in which case the long-term side effects of the newer anti-HIV drugs such as PIs need to be considered). Finally, the cost of the new combinations raises issues in both developed and developing countries concerning access to the drugs.

What is the Most Effective Initial Treatment?
The simple answer to this question is that nobody currently knows which combination of drugs is most effective at suppressing HIV replication. There are simply too many possible combinations of drugs available to test them all in clinical trials, and some of the evidence concerning the effectiveness of (particularly the newer) drugs focuses on their impact on biological markers, rather than on long-term clinical outcomes.

BHIVA guidelines in 1997 noted that optimum treatment would vary from person to person, depending on a range of different factors (**Box 6**) such as the patient's history of medical conditions, exposure to anti-HIV drugs, etc. The most recent (July 1998) update to these Guidelines (Box 6) note that data from clinical trials suggests that the most effective regimens at reducing viral replication include combinations of 2 NAs plus a PI, 2 NAs plus an NNRTI, or 2 PIs with or without NAs.

Of these, the Guidelines suggest that the use of 2 NAs with an NNRTI "*is attractive because it allows the use of PIs to be reserved for later*" (i.e. in case strains develop resistance to the initial therapy). However, this combination is only recommended for people with moderate initial viral loads (<50,000 copies/ml, see Box 6), as studies have suggested that a combination of AZT, ddI (both NAs) and nevirapine (an NNRTI) is less effective at reducing viral load from baselines above 50,000 copies/ml. The Guidelines thus recommend that patients with higher initial viral loads (>50,000 copies/ml) should be started on a PI-containing regime. This might typically be 2 NAs plus a PI, although patients with very high viral loads and very low CD4+T cell counts, or those with extensive previous exposure to NAs, might benefit more from a regime containing 2 PIs (with or without NAs).

The BHIVA Guidelines are in line with advice issued by other bodies such as USPHS and IAS, which currently favour triple combinations for initial therapy (e.g. 2 NAs + 1 PI), aimed at reducing viral load as much as possible for as long as possible. However, further research is needed to assess the relative effectiveness of different combination therapies, particularly in terms of their long-term clinical outcomes. For instance, the BHIVA guidelines pointed out that short-term data from one current study suggests that a new NNRTI (efavirenz)

BOX 6 BHIVA GUIDELINES ON ANTI-HIV TREATMENT

FACTORS GUIDING CHOICE OF DRUG COMBINATIONS
- convenience of administration / formulation
- synergistic or additive activity in the body
- lack of negative interactions in the body
- established anti-HIV activity and tolerability
- patient's history of medical conditions
- concomitant medications
- history of prior drug exposure and source of HIV infection
- central nervous system penetration
- activity in different HIV strains
- resistance pattern and possibility of limiting future therapeutic options through cross-resistance

Source: Gazzard B et al, 1997. "BHIVA Guidelines for Anti-retroviral Treatment of HIV Seropositive Individuals", Lancet 349 1086-1092

INITIATION OF THERAPY IN HIV INFECTED ADULTS
What
- viral load<50,000 RNA copies/ml, 2 NAs + an NNRTI or a PI
- viral load >50,000 RNA copies/ml, 2 NAs + 1 or 2 PIs

When
- patient agrees to treatment
- possible risks of therapy outweighed by likely benefit
- CD4 + T cell count <350/ml
- viral load value associated with risk of disease progression

Aim of therapy (in treatment naive patients)
- blood viral load to be <400-500 copies/ml and preferably <50 copies/ml by 24 weeks of therapy
- improve and extend length and quality of life

Monitoring / changing treatment
- viral load is the primary definer of treatment failure
- changes to failed treatments should be made promptly (e.g. before viral load rises to 5,000 copies/ml) and should involve a change of multiple (preferably all) drugs in the regime

Source: Gazzard B et al, 1998. "1998 Revision to the BHIVA Guidelines for Anti-retroviral Treatment of HIV Seropositive Individuals", Lancet 352, 314-316.

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looks promising. This found that 2NAs plus efavirenz were better tolerated by patients and equally as effective at reducing viral load as 2 NAs plus a PI (indinavir). BHIVA suggested that its most recent recommendations were likely to change when such drugs become more widely available.

When to Start Drug Treatment?
Some doctors, particularly in the US, advocate using the new drug treatments to 'hit' HIV infection as early and as hard as possible. The potential benefits of such early intervention are summarised in **Table 2** and include reducing the amount of damage done to the immune system and maximising the reduction in viral load. But there are also a number of potential objections to starting treatment too early (Table 2). For a start, none of the potential benefits outlined in Table 2 have actually been demonstrated in clinical trials comparing early (e.g. before the onset of HIV-related symptoms) and late (e.g. after symptoms have emerged) treatments. Other potential drawbacks are that patients might limit their future therapeutic options via cross-resistance, and that harmful side-effects might outweigh any clinical

TABLE 2 THE PROS AND CONS OF EARLY TREATMENT

Pros	Cons
It might limit the spread of HIV throughout the body (the virus actively replicates and spreads from day one of infection)	Trials of monotherapy have shown there is no clinical benefit to early treatment (due to drug resistant strains)
It might slow down the loss of CD4T+ cells and help to preserve immune function	There is no evidence from clinical trials concerning early treatment with potent triple combinations
Starting treatment when viral load is lowest might maximise the eventual reductions in viral load	Emergence of drug resistant strains might limit patient's future therapeutic options
HIV is though to be least virulent and most susceptible to drugs during the early stages of infection	The drugs' harmful side-effects might outweigh any clinical gains particularly if taken over long periods

Source: NAM HIV + AIDS Treatments Directory, 1998

advantages (particularly given that these complex combinations may have to be taken for years at a time).

Doctors in the UK have tended to be more cautious, arguing that patients may be better advised to wait until they develop symptoms, or tests show a deterioration in their CD4+T cell counts or a rise in viral load. This position is supported by the most recent BHIVA guidelines, which recommend certain thresholds at which to consider treatment (see Box 6), but which also stress the need to balance the potential benefits of early treatment against "*the potential morbidities - both physical and psychological - associated with the commitment to lifelong multi-drug therapy*".

Other Clinical Issues

While there is continued uncertainty over specific aspects of potent anti-HIV combination therapy, there is increasing evidence that the general approach is having a significant impact in reducing HIV/AIDS-related deaths and illness. For instance, a recent study of 1,255 severely immunosuppressed patients receiving treatment at clinics in the US between 1994-97, found a 75% reduction in deaths and a 73% reduction in AIDS-related illness over this period. Although the patients would have been receiving various treatments (tailored to suit their individual needs), the decline in illness and death coincided with the introduction of increasingly aggressive anti-HIV therapy into clinical practice (typically combinations of 2 NAs from 1994-96, with the addition of a PI after 1996). Results from other countries also bear witness to the success of the new treatments, but serve to highlight a number of other issues.

One of these is the problem of **long-term side-effects**. All anti-HIV drugs are known to have side-effects (these were outlined in Table 1), but the more widespread use of triple combinations over longer periods has highlighted some previously unsuspected problems thought to be linked to the PIs. These include changes in body shape and fat distribution (lipodystrophy), increasing levels of

BOX 7 UK SPENDING ON HIV/AIDS

Treatment and care - the Department of Health (DH) have allocated a total of £228.4M for HIV/AIDS treatment and care in England and Wales in 1998/99. This includes an extra £23M specifically allocated to help the NHS provide combination drug therapies. In Scotland, £9.6M was earmarked for treatment and care in 1997/98, but this figure excludes additional resources that individual Health Boards may commit from their general allocations.
Prevention -the HIV/AIDS prevention budget (for testing, infection control, health education, etc.) for 1998/99 is £53.4M.
Research - the Medical Research Council (MRC), DH and other Government Departments spend on HIV/AIDS research in 1997/98 is estimated at £18.1M.
Other spending - DH spent an additional £4.2M in 1996/97 on HIV/AIDS related health initiatives, campaigns and helplines.

fats (hyperlipidemia) in the blood (leading to long-term concerns over increased risk of cardiovascular disease) and problems with blood sugar levels and diabetes. Such side-effects may jeopardise adherence to drug regimes, and also influence risk / benefit calculations over when to start treatment (particularly in people with HIV who are currently free from symptoms). Other clinical issues include:

- What to do if treatment fails? The new combination treatments do not always work, and research is required into reasons for failure (non-adherence, cross-resistance), when to change therapy (if viral loads or CD4+T cell counts change), the best salvage therapies (BHIVA guidelines recommend that failed drug regimes should be changed by at least two drugs) and how to prevent failures in the first place.
- The need for better treatments. Researchers point out that the new drugs are not a cure for HIV/AIDS, and see an urgent need for more effective, more user friendly (e.g. single dose per day) drugs.
- The need for better information on the viral status of people on anti-HIV drug treatments (e.g. what are the risks of people whose viral load is below detectable levels transmitting the virus?).

UK Research

To what extent is UK research addressing the needs identified above? The most recent edition of the National Aids Manual lists more than 20 on-going clinical trials involving UK patients assessing anti-HIV treatments. Many of these are relatively short-term protocols assessing impacts on biological markers for licensing purposes. As outlined in **Box 7**, the total UK spend on HIV/AIDS research in 1997/98 is estimated at £18.1M, most of which is provided through the MRC. The MRC HIV Clinical Trial Centre is co-ordinating a number of major trials and these include:

- PENTA 5 - a multi-centre trial assessing combinations of NAs (two out of AZT, 3TC and a new drug, abacavir) and a PI (nelfinavir) in children.
- PROCOM - (Protease Combinations), an exploratory

UK study assessing 'subtractive' therapy in adults. Initial treatment will be with an aggressive 4 drug combination - 2PIs (saquinavir and nelfinavir) and 2 NAs (ddI + d4T) - but once viral loads have dropped below detectable levels, some patients will have drugs subtracted (e.g. receiving just 2 PIs).

- ADHOC - (Adefovir Dipivoxil for HIV or CMV), a trial assessing the safety and activity of a new drug (AD), taken alongside existing anti-HIV treatments.
- INITIO - a new trial currently being planned to investigate different combination therapies (2 NAs + NNRTI + PI versus 2NAs + NNRTI versus 2 NAs + PI).

Research is also continuing into other approaches, such as the search for effective vaccines (both therapeutic and preventative) and ways of boosting the immune system to help fight HIV in the body (MRC is currently planning a trial with the US National Institutes of Health assessing the immunostimulant IL2).

One issue not currently being addressed is the question of when best to start treatment. In principal, this could be resolved by a clinical trial comparing early and late starts to treatment, and the MRC has been considering conducting such a trial for some time. However, in practice there are inherent difficulties in designing a trial of this type, since people with HIV generally wish to choose when their treatment starts, rather than being randomly allocated to early or late treatment. This issue was the subject of discussion at the recent World HIV/AIDS conference in Geneva, where the emerging view favoured the more cautious approach, because of increasing evidence of the serious side-effects of combination therapy, difficulties with compliance, cross-resistance, etc.

Access to Drugs
The complexity of current triple combination treatments means that they are very expensive, in the region of £10,000-£15,000 per patient per year. The total HIV/AIDS treatment and care budget (Box 7) in England and Wales is £228.4M (this includes an extra £23M specifically allocated to help provide anti-HIV drugs) and £9.6M in Scotland. At present, there are 30,000 or so known HIV positive people in the UK (including those with AIDS), around 13,000 of whom are currently receiving treatment. This proportion is likely to increase in the coming years, as currently healthy HIV positive individuals show signs of disease progression and elect to start treatment.

Although doctors do not know how long the new combination therapies will continue to suppress viral replication, current indications suggest that they may do so for a number of years. The new anti-HIV drugs may thus carry significant cost implications for the NHS in the future (treating all of the 30,000 or so known UK individuals with HIV/AIDS with triple combination therapy would cost the NHS £300M-£450M per year).

While this could strain the health budgets of developed countries, the situation is even worse for those developing countries which have borne the brunt of the HIV/AIDS epidemic. UNAIDS is attempting to organise routes by which subsidised anti-HIV drugs could be made available to developing countries. However, the complexity of existing treatments means that developing countries lack the infrastructure (viral load testing, support to encourage adherence to drug regimes, etc.) to use them effectively, even if the drugs were supplied free of charge. Trials involving less complex and expensive drug regimes have been conducted, although some claim that it is unethical to trial inexpensive but sub-optimal treatments in Africa that would not be allowed in the US or Europe. Such problems have highlighted the need for simpler and more effective treatments (e.g. therapeutic vaccines, simpler drug combinations) and preventative approaches (e.g. viricides, preventative vaccines).

UK National Strategies for HIV/AIDS
In December 1997, the Minister of State for Public Health announced a proposal to draw up national strategies for HIV/AIDS. The 'Our Healthier Nation' Green Paper in February 1998 set out a broad framework for action on public health issues at a national level, and also proposed the need for local targets to address issues such as HIV/AIDS that affect some parts of the country more than others. These strategies will be formulated by a Steering Group taking into account responses to the consultation exercise and the outcome of a conference of experts and stakeholders planned for September 1998. This will cover the full range of HIV /AIDS related issues including research and development, prevention, treatment and services, etc.

The All Party Parliamentary Group on AIDS (APPGA) held a series of Parliamentary Hearings in July 1998 focusing on the question of how the Government can respond to the changing needs of people with HIV/AIDS and how national strategies can be devised to meet these needs. These included a wide range of issues covering the current state of the epidemic, HIV prevention, treatments (including access to drug therapy), and how to make national strategies work. One of the aims was to inform the development of national strategies on HIV/AIDS, and the outcome of the APPGA Hearings will be published in a report timed to feed into the planned DH conference in September 1998.