Aspects of HIV infection and treatment

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Educational aims

- To familiarize pharmacists with the management of HIV
- To provide an overview of anti-retroviral therapy
- To highlight issues related to adherence and interactions

Key words
HIV, highly active anti-retroviral therapy (HAART), viral load, CD4 count, adherence.

Anti-retroviral therapy in the treatment of HIV (human immunodeficiency virus) aims to lower the viral load and improve immune function. Numerous interventions in the management of HIV seropositive patients are aimed to maximise individual patient adherence to treatment.

Introduction

The HIV pandemic has far exceeded projections over the past decade. At the end of 2008 there were:

- an estimated 33.4 million people living with HIV worldwide,
- an estimated 2.7 million new HIV infections, and
- an estimated 2.0 million AIDS (acquired immunodeficiency syndrome)-related deaths.[1]

With regards to the local scenario, there were 30 new HIV infections and one AIDS-related death in Malta, in 2008.[2] In Malta, HIV testing is totally confidential, and is available free of charge to anyone.[3] All patients are given a unique code number and only this number appears on all request forms. This procedure is used to eliminate the true identity of patients throughout the process – thus protecting confidentiality.

Aetiology and pathology of HIV

HIV is a retrovirus that infects cells of the immune system, leading to a specific decline in the CD4+ helper T cells. Immune responses to certain antigens begin to decline, and the host fails to adequately respond to opportunistic infections and normally harmless commensal organisms.

The widespread use of anti-retroviral therapy has had the most profound influence on reducing opportunistic infection-related mortality in HIV-infected persons. However, opportunistic infections remain a leading cause of morbidity and mortality in HIV-infected persons.

Anti-retroviral therapy

The goal of anti-retroviral therapy in HIV infection is to increase the length and quality of life by improving immune function. This is achieved by reducing the amount of replicating virus to as low a level as possible, for a long as possible, in all sites where HIV-infected cells are present, thereby preventing infection of new cells and further damage to the immune system. The amount of replicating virus in the plasma can be assayed by measuring the concentration of HIV RNA, referred to as the viral load. In practical terms, the aim of anti-retroviral therapy is to lower the viral load to a value below the level of detection of the assay used. Achieving this with the currently available anti-retroviral agents involves appropriate selection of combination regimens to obtain an antiviral response, and excellent adherence to the regimen by the patient. In addition, consideration of a plan for salvage or second line regimen is required if initial therapy fails.

There are eleven anti-retroviral agents currently being used in Malta (Table 1). These can be divided into three classes:

1. Nucleoside reverse transcriptase inhibitors (NRTIs)
   These were the first drugs to be licensed for the treatment of HIV infection. They are generally considered to be the backbone of anti-retroviral therapy when combined with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).
2. Protease inhibitors (PIs)
   A dramatic decline in the clinical progression of HIV disease and HIV-related deaths followed the introduction of PIs. The main drawbacks to PIs are the number of dose units that patients have to take, and the need for food restrictions.
3. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
   These are the third class of drugs currently available to treat HIV infection. They are generally considered simpler to take than PIs, but are hampered by the fact that resistance develops quickly, and patients are usually resistance to all drugs within the class.

These drugs act at different stages in the

Table 1. Anti-retroviral agents used locally	
NRTIs	Didanosine Lamivudine Stavudine Tenofovir Zidovudine
PIs	Indinavir Lopinavir/ritonavir Ritonavir Saquinavir
NNRTIs	Efavirenz Nevirapine

HIV replication cycle. The first anti-retroviral agent to become commercially available was zidovudine in 1987, followed by didanosine and zalcitabine in 1993 – all of which are NRTIs. Initially, these drugs were used alone as mono-therapy (often sequentially, as each agent became available). It is now realized that rapid resistance develops to anti-retroviral drugs if they are not used in combination. Effective combination therapy consisting of three or more anti-retroviral drugs, or highly active anti-retroviral therapy (HAART), is now the accepted standard of care for HIV-infected individuals requiring treatment.

Initiation of treatment

The CD4+ T-cell count (or CD4 count) serves as the major clinical indicator of immune function in patients who have HIV infection. It is one of the key factors in deciding whether to initiate antiretroviral therapy and chemoprophylaxis for opportunistic infections, and is the strongest predictor of subsequent disease progression and survival.

Most major guidelines (British, European and American guidelines) agree that antiretroviral therapy should be initiated in all patients with a CD4 count <350 cells/mm[3. 4, 5, 6]

Importance of strict adherence to treatment

HIV treatment is a chronic treatment and an expensive one too. Furthermore, strict adherence to an already complicated regimen is vital. Numerous international studies have concluded that less than 95% adherence is equivalent to treatment failure. Since most anti-retroviral drugs currently available exhibit cross resistance, development of resistance to a drug often means resistance to the entire class of drugs, thus limiting future treatment options.

It is fair to say that HIV infection is no longer considered the terminal illness that it was 5 to 10 years ago, but it is now regarded as more of a chronic infection, manageable with antiviral therapy. However, current knowledge indicates that the therapy should be for life, a situation that makes the issue of adherence a real obstacle for some patients.

A thorough understanding of HIV therapy, including the importance of good adherence and the dangers of poor adherence, is an important basic tool to increasing adherence. The importance of adherence is always stressed to all patients, including all new patients prior to initiating therapy.

Learning the patient's daily routine and incorporating dosing cues into that routine is a very helpful tool to increase adherence. Patients are actively encouraged to discuss any problems with fitting their daily doses with their daily activities.

Partial adherence is extremely common. When assessing adherence of patients already on treatment, a neutral approach to adherence history is preferred. Questions like: "How many doses have you missed or taken more than an hour late, in the past month?" are preferred to "Have you taken all medications as instructed?"

New patients are informed that this new medication schedule might seem a bit complex initially, but they would eventually learn to fit it into their daily routine — and it will feel less complex.

Two typical regimens that are currently being used in the treatment of HIV involve:

- Lopinavir/ritonavir 200/50mg tablets, two tablets 12 hourly
- Zidovudine/lamivudine 300/150mg tablets, one tablet 12 hourly

OR

- Efavirenz 600mg tablets, one tablet nocte
- Tenofovir 245mg tablets, one tablet daily
- Lamivudine 150mg tablets, one tablet 12 hourly

Effects and side effects of medication

Anti-retrovirals are not a cure for HIV – however, they can help reduce the chances of getting opportunistic infections associated with HIV. This fact is clearly explained to all patients – it is considered to be of utmost importance that all patients are aware that HAART does not kill the virus, but suppresses it to a minimal level.

As a consequence, patients are made aware that they can still transmit the virus to others. All HIV-infected patients (even those with viral loads below detection limits) are counseled to avoid sexual and drug-use behaviors that may lead to transmission or acquisition of HIV or other pathogens.

The pharmacist goes over the important beneficial effects and side effects of every

Table 2. Some common side effects of anti-retroviral drugs

Drug	Side effect	Management of side effect
Zidovudine	Anaemia	Change to another NRTI with less incidence of this adverse event (e.g.) tenofovir
Indinavir	Crystalluria Hypercolesterolaemia	Change to another PI with less incidence of this adverse event (e.g.) lopinavir/ritonavir
Efavirenz	Rash Psychiatric symptoms	Change to another agent from the same class or a different class (e.g.) nevirapine or lopinavir/ritonavir

medication the patient is taking. Potential common and severe adverse effects that may occur, and actions to prevent or minimize their occurrence, are always discussed.

For example, a patient initiating therapy with zidovudine is extensively counseled on the gastrointestinal adverse effects that are likely to occur, especially during the first weeks of therapy. Such information can greatly increase adherence to the regimen.

Patients are also advised about proper storage of all medication, for example, ritonavir should be kept in a fridge especially in our hot summer months.

Potential for drug interactions

The importance of considering the potential for drug interactions in patients receiving HAART cannot be overemphasized. Drug–drug interactions may involve positive or negative interactions between antiretroviral agents or between these and drugs used to treat other coexistent conditions.

Clinically important interactions to consider when co-administering with antiretroviral drugs include interactions with the following drugs:

- methadone
- oral contraceptives (oestrogen-containing)
- anti-epileptics
- antidepressants
- lipid-lowering agents
- acid-reducing agents
- certain antimicrobials (e.g. clarithromycin, minocycline and fluconazole)
- some anti-arrhythmics
- tuberculosis therapy
- anti-cancer drugs
- immunosuppressant
- phosphodiesterase inhibitors
- anti-hepatitis C therapies

Many of these interactions are manageable (i.e. with/without dosage modifications, together with enhanced clinical vigilance) but in some cases (e.g. rifampicin and PIs) and didanosine and ribavirin (used in hepatitis C), the nature of the interaction is such that co-administration must be avoided.

The busy healthcare professional can turn to the local drug information pharmacists when seeking to check for potential drug interactions. In addition, the University of Liverpool's comprehensive drug interaction website[7] is an excellent and highly recommended resource.

Practice points

- The goal of anti-retroviral therapy in HIV infection is to increase the length and quality of life by improving immune function.
- The three main classes of anti-retrovirals are nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).
- HIV is a chronic infection, treatment of which necessitates very strict adherence (>95%).
- The pharmacist plays a major in offering support to ensure maximal adherence.
- Pharmacists must always be on the look out for any potential adverse events and drug interactions when anti-retrovirals are taken in conjunction with other mediations.

Conclusion

With the dramatic decrease in opportunistic infections brought about by the standard use of HAART, the care of patients infected with HIV has largely been transferred to the outpatient setting. Consequently, community pharmacists will be increasingly involved in the outpatient care of HIV-infected patients by ensuring patient adherence to complex treatment regimens and providing pharmaceutical care.

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