Antiretroviral Combination Therapy for HIV Infection

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Abstract: **Since the introduction of highly active antiretroviral therapy, studies have demonstrated declining morbidity and mortality rates among people with HIV. This is largely because antiretroviral combination therapy can suppress plasma HIV viral load below detectable limits and cause gradual elevation in CD4 cell counts, resulting in improved immune status for responsive patients who are compliant with therapy. These drugs, however, are not without side-effects, both general and oral, and this review draws attention to some of the interactions of the drugs used to treat HIV infection with drugs used in dentistry.**

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Clinical Relevance: **As the number of people living with HIV increases there will be an increase in their healthcare needs, including oral healthcare. Dental professionals have the responsibility to provide the best oral care possible to this growing population and to be well informed about the current treatments for HIV.**

A combination of medication, aimed at retarding the reproduction of the human immunodeficiency virus (HIV), early diagnosis, improved treatment of opportunistic infections and improved medical management has resulted in increased survival time and a changing clinical pattern for people with HIV. The number of people developing AIDS and the number of deaths from HIV disease has decreased since the introduction of highly active antiretroviral therapy (HAART) in 1996 (Figure 1).

This effect, combined with continued new HIV diagnoses, has led to an increased prevalence of diagnosed infections. Over 25 000 people are now living with HIV in the UK.[1] At the same time, patients with a newly improved outlook on survival may place renewed importance on oral healthcare to enhance their quality of life.[2]

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IMMUNOLOGY

It is now over 20 years since the first cases of acquired immune deficiency syndrome (AIDS) were reported in the USA. HIV causes a progressive disease, in which the regulation and function of the immune system are impaired. There is no cure for infection caused by HIV.

HIV is an RNA retrovirus; its genetic material is contained in RNA rather than DNA (Figure 2). The virus attaches to and enters the CD4-positive T lymphocytes, where the viral RNA uses the cell's enzyme reverse transcriptase to produce DNA copies of itself. The CD4 cells lose their normal function and are reduced in number. The depletion of these cells is a widely used marker for disease progression and prognosis and is associated with the development of opportunistic infections.

As measured by flow cytometry, normal CD4 counts range from 600 to 1600 cells/mm^3 of blood, with a median count of 1000 cells/mm^3. Initial immune suppression is indicated by CD4 levels below 500/mm^3 and signals the first appearance of systemic and oral opportunistic infections. Two key laboratory tests are used to assess HIV disease progression and monitor the success of HAART:

- measurement of CD4 cell counts;
- quantification of plasma viral load.

These approaches provide vital information on immune suppression and the rate of virus replication within the blood.

Viral loads are often expressed in logarithms ($\log_{10}$) because of the relatively large ranges of HIV RNA values. The viral load is reported as undetectable or below the limit of detection if the copy number is below the lower threshold of assay detection. This does not mean that the virus has been removed from the body but that numbers are suppressed to a very low level in the plasma. A change in HIV RNA concentration of more than three-fold in either direction is considered a biologically relevant change in the level of viral replication. In general, the CD4 cell count and HIV RNA load are inversely correlated with one another. Viral replication is detectable a few weeks after exposure and can peak at extremely high levels shortly thereafter. During this period of primary infection, peak viral load is accompanied by an abrupt decline in the number of circulating CD4 cells.[2]

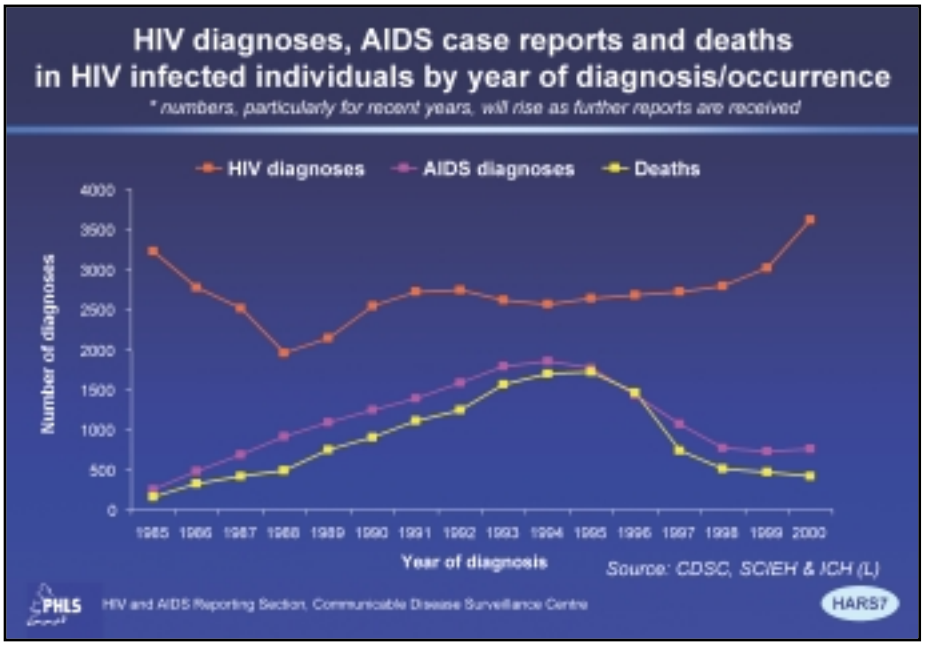

Figure 1. *HIV diagnoses, AIDS case reports and deaths in HIV-infected individuals by year of diagnosis/occurrence in the UK (Public Health Laboratory Service, 2001).*

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

Drugs in combination therapy work in different ways and at different parts of the HIV life cycle (Figure 3).[3]

Drugs currently licensed in the UK for treating HIV infection are inhibitors of either reverse transcriptase or protease. They are toxic and expensive but they maintain physical and mental health and increase life expectancy. HAART can slow or reverse the loss of CD4 cells that is a hallmark of HIV infection.

With the introduction of antiretroviral medication, a change in the epidemiology of opportunistic infections such as *Pneumocystis carinii* pneumonia (PCP), oral and oesophageal candidosis and Kaposi's sarcoma has occurred.[4]

Oral lesions have been found to be declining in prevalence in HIV-infected individuals. Oral lesions strongly associated with HIV such as hairy leukoplakia, oral candidosis, Kaposi's sarcoma and necrotizing ulcerative periodontal disease are also strongly associated with decreasing CD4 cell counts. Problems with adherence to medication and prevalence of drug-resistant infections among people with HIV may affect current and future trends in prevalence of oral lesions.[5]

HAART has been shown to produce *in vitro* improvement in T lymphocyte function. The observation of reduction in prevalence of oral lesions that are partially immune mediated seems accurate because HAART can restore CD4 counts, and these CD4 lymphocytes are important in host defence against opportunistic organisms such as Epstein–Barr virus (the aetiological agent of hairy leukoplakia) and *Candida* species.[5] Kaposi's sarcoma is less common clinically than in pre-HAART days.[6]

PRINCIPLES OF ANTIRETROVIRAL THERAPY

Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible. It should be started before the immune system is irreversibly damaged. The need for early drug treatment should be balanced against the development of toxicity. The recognition that combining highly active antiretrovirals can reduce plasma viral load to below the level of detection has transformed the management of HIV over the last 5 years.

However, the virus continues to evolve and mutate even when the viral load is at very low levels. The development of drug resistance is reduced by using a combination of drugs, but such combinations should have synergistic or additive activity whilst ensuring that their toxicity is not additive.[7]

Many patients encounter practical difficulties owing to the number of pills that need to be taken daily and the complexity of treatment regimens.

Nucleoside Analogues

Zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI) or nucleoside analogue, was the first anti-HIV drug to be introduced. Others include abacavir, didanosine, lamivudine, stavudine and zalcitabine. These slow down replication of HIV.

Combinations of zidovudine and lamivudine are manufactured as Combivir, and Trizivir (a combination of zidovudine, lamivudine and abacavir) is now available in the UK as one tablet. This potent combination of three proven NRTIs in one simple-to-take tablet is designed to make living with antiretroviral treatment easier than with current regimens. Lamivudine is also licensed for use in combination with interferon-alpha for chronic hepatitis B infection.

As nucleoside analogues are included in human DNA they interfere with normal cellular metabolism and can lead to toxicity.

Non-nucleoside Analogues

Non-nucleoside analogues or non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit reverse transcriptase but in a different way to nucleoside analogues. The latter act as false substrates and trick the enzyme into

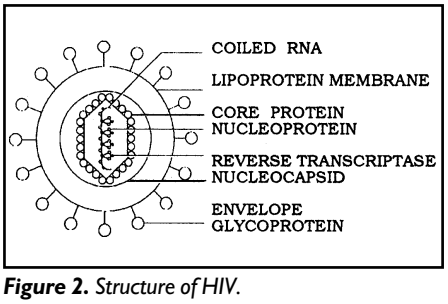

Figure 2. *Structure of HIV.*

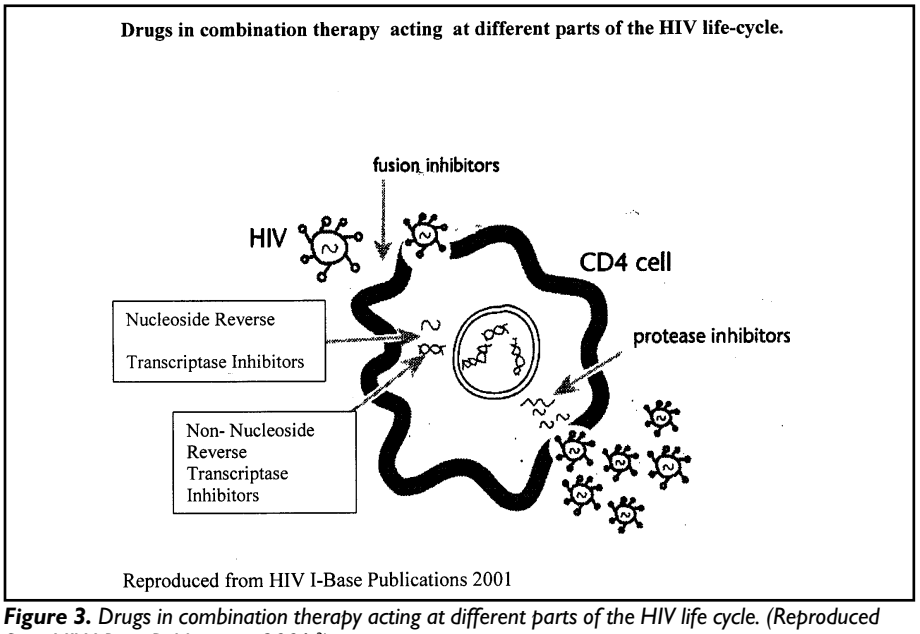

Figure 3. *Drugs in combination therapy acting at different parts of the HIV life cycle. (Reproduced from HIV I-Base Publications 2001.[3])*

incorporating them into DNA. In contrast, the non-nucleoside analogues bind directly to the enzyme, changing its structure. This means the enzyme is no longer able to bind to the nucleotides, which inhibits HIV replication.[8]

Efavirenz (Sustiva) and nevirapine (Viramune) are the only drugs licensed at present.

Protease Inhibitors

These work at a different part of the HIV replication cycle than reverse transcriptase inhibitors. They bind reversibly to the active site of HIV protease and competitively inhibit the enzyme, thereby preventing the cleavage of viral precursor polyproteins that occurs during maturation of newly formed viral particles. The resulting immature particles are non-infectious and are incapable of establishing new cycles of infection.[9]

The arrival of the protease inhibitors indinavir, ritonavir, saquinavir and nelfinavir resulted in an almost immediate fall in reported cases of the three major opportunistic infections PCP, MAC and cytomegalovirus (CMV); there was also a decrease in the number of new cases of AIDS.[10]

Certain micronutrients, such as zinc and magnesium, may augment the outcome of HAART and possibly attenuate side effects.[11]

Pregnancy

A short course of zidovudine has been shown to halve the rate of mother to child transmission of HIV.

SIDE EFFECTS OF ANTIRETROVIRAL DRUGS

All of the antiretroviral agents have been associated with side effects, many of which can be managed symptomatically. Side effects of the NRTIs are mainly gastrointestinal (e.g. nausea and vomiting), although malaise, fatigue, headache and peripheral neuropathy have also been reported. The side effect profile of the NNRTIs is more favourable.

- Nevirapine can cause liver toxicity and severe rashes, and sometimes Stevens–Johnson syndrome.
- Efavirenz causes neurological side effects, with mood disturbances, disturbed sleep patterns and vivid dreams but has a lower incidence of rash, which is also generally less severe.
- Ritonavir is poorly tolerated, and has a high incidence of nausea, diarrhoea, vomiting, abdominal pain, peripheral paraesthesia and headache.
- Saquinivir is better tolerated but has similar side effects. High incidence of side effects at the start of therapy has been attributed to the high plasma concentrations that are seen.[9]
- Nelfinavir causes diarrhoea and may accelerate clearance of oral contraceptives, resulting in reduced contraceptive efficacy.
- Protease inhibitors have been reported to cause diabetes mellitus, and may exacerbate existing disease.
- Kidney stones, haemolytic anaemia, dry skin and hair loss have been reported in patients taking indinavir.[9]
- Many HAART drugs have oral side effects (Table 1).

Lipodystrophy

Lipodystrophy is increasingly being reported as a side effect of antiretroviral treatment. Levels of fat and sugar in the blood are affected, body shape changes and the distribution of body fat alters. The protease inhibitors and NNRTIs appear to cause fat accumulation to stomach, breasts and across the shoulders, whereas the NRTIs have been linked with fat loss from arms, legs, face and buttocks.

Early symptoms are often reversible if

Oral side effect	NRTI	NNRTI	Protease inhibitors
Dry mouth	Didanosine		Indinavir, ritonavir
Oral ulceration	Zalcitabine		Saquinavir, ritonavir
Taste disturbances	Zalcitabine		Indinavir, ritonavir
Pigmentation of the oral mucosa	Zidovudine		
Circumoral paraesthesia	Didanosine		Ritonavir
Stevens–Johnson syndrome with oral lesions		Nevirapine	

Table 1. *Oral side effects of antiretroviral drugs.*

Presentation	Surrogate markers	Recommendations
Primary HIV infection	Any CD4 level	If treatment considered, start as soon as possible, preferably within 6 months of contracting HIV
Asymptomatic HIV infection	CD4 count >350 cells/µl at any viral load	Defer treatment
	CD4 count 200–350 cells/µl with a viral load <100 000 copies/ml	Start treatment, taking into account the rate of CD4 decline, symptoms, patient's wishes
	CD4 count < 200 cells/µl, any viral load	Start treatment
Symptomatic HIV infection	Any CD4 level	Treat

Table 2. *Guidelines on the use of anti-HIV drugs by adults.*[12]

drugs are switched, and exercise and diet can help.[3]

RESISTANCE

Resistance to anti-HIV drugs occurs when the virus mutates, and if the viral load remains high after 3–4 months treatment should be changed. Resistance may occur to more than one drug in the same family. Drug resistance is a major cause of HAART failure and several studies have documented that resistant HIV can quickly emerge when viral suppression is incomplete, whether due to prior resistance, poor adherence, poor drug pharmacokinetics or other regimen problems.

DRUG INTERACTIONS

Many of these medications are eliminated from the body by the same route, leading to varied drug interactions.

- The plasma concentrations of diazepam and midazolam are increased when co-administered with efavirenz, saquinavir and ritonavir. This brings a risk of extreme sedation and respiratory depression and concomitant use should be avoided.[9] This has implications for management of people who may benefit from intravenous sedation for their dental treatment.
- St John's Wort reduces the plasma concentration of protease inhibitors.
- Ritonavir oral solution contains 43% ethanol; therefore concomitant administration with disulfiram or drugs with disulfiram-like reactions (e.g. metronidazole) should be avoided. This reaction is less likely with ritonavir capsules.[9]
- Saquinivir is a weak inhibitor of cytochrome P_{450} and has the potential to increase plasma concentrations of drugs which share this method of elimination (e.g. clindamycin, erythromycin, fluconazole, dexamethasone, fentanyl and alfentanil).[9]

INITIATION OF THERAPY

The optimum time for initiation of antiviral treatment will depend on the CD4 cell count, the plasma viral load and clinical symptoms. The period before complete seroconversion, which is often symptomatic, is called primary HIV infection.

The British HIV Association (BHIVA) has attempted to provide consensus across a range of healthcare workers including physicians, virologists, people living with HIV and special-interest voluntary organizations, stressing that treatment should begin before irreversible damage to the immune system occurs. The BHIVA has produced guidelines on the use of anti-HIV drugs by adults:[12] treatment should begin when the benefits of the available treatment outweigh the risk of not starting. The theoretical advantage of starting early treatment is balanced against uncertainty of efficacy, considerations of adherence to long-term therapy, potential toxicity and development of drug resistance. Recommendations for treatment are continually under review;[12] the current recommendations are shown in Table 2. Individuals with rapidly declining CD4 counts (>80 cells per year), rapidly rising viral loads or a high viral load (over 100 000 copies) should be monitored closely every 2–3 months.

The BHIVA recommend early treatment with a combination of at least three drugs: treatment within the first 6 months of contracting HIV may provide a unique window of opportunity for treating the virus when it is most vulnerable and the immune system is strongest. Regular measurement of viral load and CD4 levels are vital in reducing viral load to below the level of detection; failure to achieve or sustain this control should prompt modification of therapy, with substitution or addition of at least two agents.

Drug Combination

There are a number of options for antiretroviral regimens:

- a protease inhibitor with low-dose ritonavir (to improve pharmacokinetics) plus two NRTIs;
- two protease inhibitors plus two NRTIs;
- a NNRTI plus two NRTIs.

For people starting anti-HIV treatment for the first time, a combination of two NRTIs and one NNRTI is recommended. The best evidence is for a protease inhibitor plus two NRTIs, but data is emerging on the other combinations.

The risks and benefits of starting treatment should be based on the risk of disease progression (judged by viral load and CD4 count[12]) and long-term side effects such as lipodystrophy and diabetes. Cardiovascular risk factors should be assessed before starting treatment as raised cholesterol and triglyceride levels may be side effects of treatment.

Earlier treatment may limit the progressive destruction of the immune system and reduce the subsequent risk of

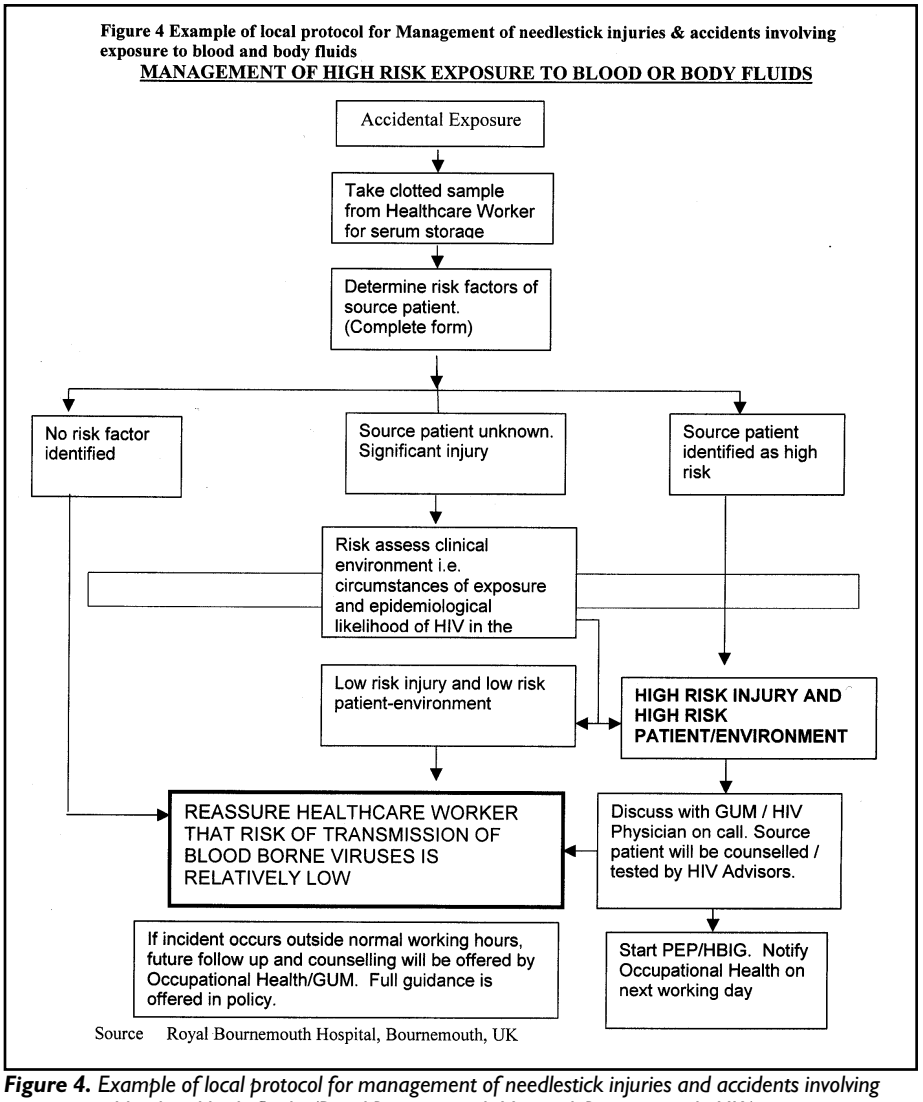

Figure 4. *Example of local protocol for management of needlestick injuries and accidents involving exposure to blood and body fluids. (Royal Bournemouth Hospital, Bournemouth, UK.)*

infection by opportunistic pathogens such as *Mycobacterium tuberculosis* and development of tumours such as Kaposi's sarcoma.

Dental practitioners must be aware of the potential for drug interactions and should seek advice from the patient's HIV physician before undertaking treatment that involves drug prescription.[13]

Adherence to Therapy

In order to maximize adherence, particular attention should be paid to potency, tolerability, potential toxicity, likely drug–drug interactions and the psychological burden of life-long therapy. The regimen should be tailored to each individual patient. Adherence diaries might be helpful.[3]

POST-EXPOSURE PROPHYLAXIS

Treatment with antiviral drugs may be appropriate following occupational exposure to material contaminated with HIV. Guidance from the UK Chief Medical Officers' Expert Advisory Group on AIDS[14] recommends initial risk assessment and consideration of the issue of post-exposure prophylaxis (PEP) based on the type of body fluid or substance involved and the route and severity of the exposure.

For optimal efficiency, PEP should be commenced as soon as possible after the incident – ideally within the hour. Starter packs of antiretroviral therapy must be available in Occupational Health and Accident and Emergency departments. Clear protocols for post-exposure assessment, management and prescription of PEP must be in place (Figure 4).

Zidovudine (NRTI) is the only drug for which there is currently evidence of a reduction of risk of HIV transmission following occupational exposure. No antiretroviral has been licensed for PEP. These drugs can be prescribed for PEP only on an off-label basis since their use in this context is outside approved indications. Recommended drugs are:

- Zidovudine 200 mg tds or 250 bd
- *plus* lamivudine 150 mg bd
- *plus* nelfinavir 750 mg tds or 1250 mg bd.

All dentists and their teams should be informed of the whereabouts of their locally agreed PEP protocol and access to relevant advice and treatment ensured.

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