A balance of risks for the treatment of the chronically HIV-infected asymptomatic individual

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Highly active antiretroviral therapy (HAART) has had a dramatic impact on the morbidity and mortality associated with HIV infection. Death rates fell by 70% between 1995 and 1997 following its introduction.[1] It remains difficult to decide when to start therapy in the asymptomatic individual. The benefits of starting therapy in reducing the short-term risk of AIDS and mortality at any given CD4 count must be balanced against the harm from deferring therapy, as well as drug toxicity and tolerability, drug resistance and the ability of the individual to adhere to the regimen. The current British HIV Association (BHIVA) guidelines recommend that patients start therapy before the CD4 count falls below 200 cells/μl. Treatment is not currently indicated in asymptomatic individuals with a CD4 count above 350 cells/μl. In patients with a rapidly falling CD4 count (200–350 cells/μl) or a high viral load (>55,000 copies/ml) treatment may be considered at an earlier stage.[2]

Historical perspective of antiretroviral therapy

Zidovudine as monotherapy was the first antiretroviral drug to be introduced in the management of HIV infection in 1987. It had a marked effect on both mortality and the development of AIDS, but only transiently and only in symptomatic HIV-infected patients.[3,4] Further studies showed the superiority of dual therapy over monotherapy in reducing mortality in both asymptomatic and symptomatic individuals.[5] In 1997, data from a controlled trial showed that treatment with the combination indinavir, zidovudine and lamivudine slowed progression of HIV-1 disease in patients with CD4 counts below 200 cells/μl more than dual therapy with zidovudine and lamivudine, despite prior exposure to zidovudine.[6] Reductions in morbidity and mortality were clearly linked to the intensity of treatment, with combinations of three drugs, including a protease inhibitor (PI), showing the most benefit at that time.[1] Subsequently, an open-label study found that the combination of efavirenz (a non-nucleoside reverse transcriptase inhibitor (NNRTI)), zidovudine and lamivudine had equal or superior antiviral activity and was better tolerated than the combination of indinavir, zidovudine and lamivudine.[7] Further research has enabled the development of potentially simpler regimens and has also broadened the options available to the antiretroviral-naïve individual. The term 'HAART' is used to describe a regimen of three or more antiretroviral drugs. Studies of four- versus three-drug regimens have suggested that any possible increase in efficacy by the addition of another drug is likely to be tempered by the additive toxicity associated with the use of further agents.

As outlined below, the wider use of antiretroviral agents has led to a better understanding of their limitations and a re-think of the 'hit hard, hit early' paradigm proposed after the advent of HAART.

When to start HAART? (Table 1)

There are no randomised controlled trials on the question of when to start HAART. The current recommendations have been largely based on a number of cohort studies:

Plasma viral load strongly predicts the rate of decline in CD4 cells and progression to AIDS and death without HAART. It is of prognostic significance if individuals have a viral load over 100,000 copies/ml before starting HAART.[8–10]

CD4 count is of prognostic significance regardless of whether or not the person is on HAART. There is a greater risk of disease progression to AIDS and death or death without AIDS in patients starting HAART with a CD4 count below <200 cells/μl.[9,11] There are immunological and virological advantages in starting HAART at a CD4 count of 200–350 cells/μl, but no clinically significant additional benefit at a CD4 count above 350 cells/μl. Studies suggest that the rise in CD4 count in patients starting HAART is similar, regardless of their pre-HAART CD4 level. Once the CD4 count is above 200 cells/μl a patient has a low risk of a subsequent AIDS-defining illness or death. The rate of virological

Table 1. Current British HIV Association (BHIVA) recommendations.[2]

Presentation	Surrogate markers	Recommendation
Primary HIV infection		If treatment considered, start as soon as possible, certainly within 6 months of contracting HIV, and as part of a clinical trial if available
Established asymptomatic HIV infection	CD4 count >350 cells/μl and any viral load	Defer treatment
	CD4 count 200-350 cells/μl	Start treatment, taking into account the rate of CD4 decline, symptoms, patient's wishes and viral load
	CD4 count <200 cells/μl and any viral load	Treat
AIDS or serious/recurrent/ HIV-related illness		Treat

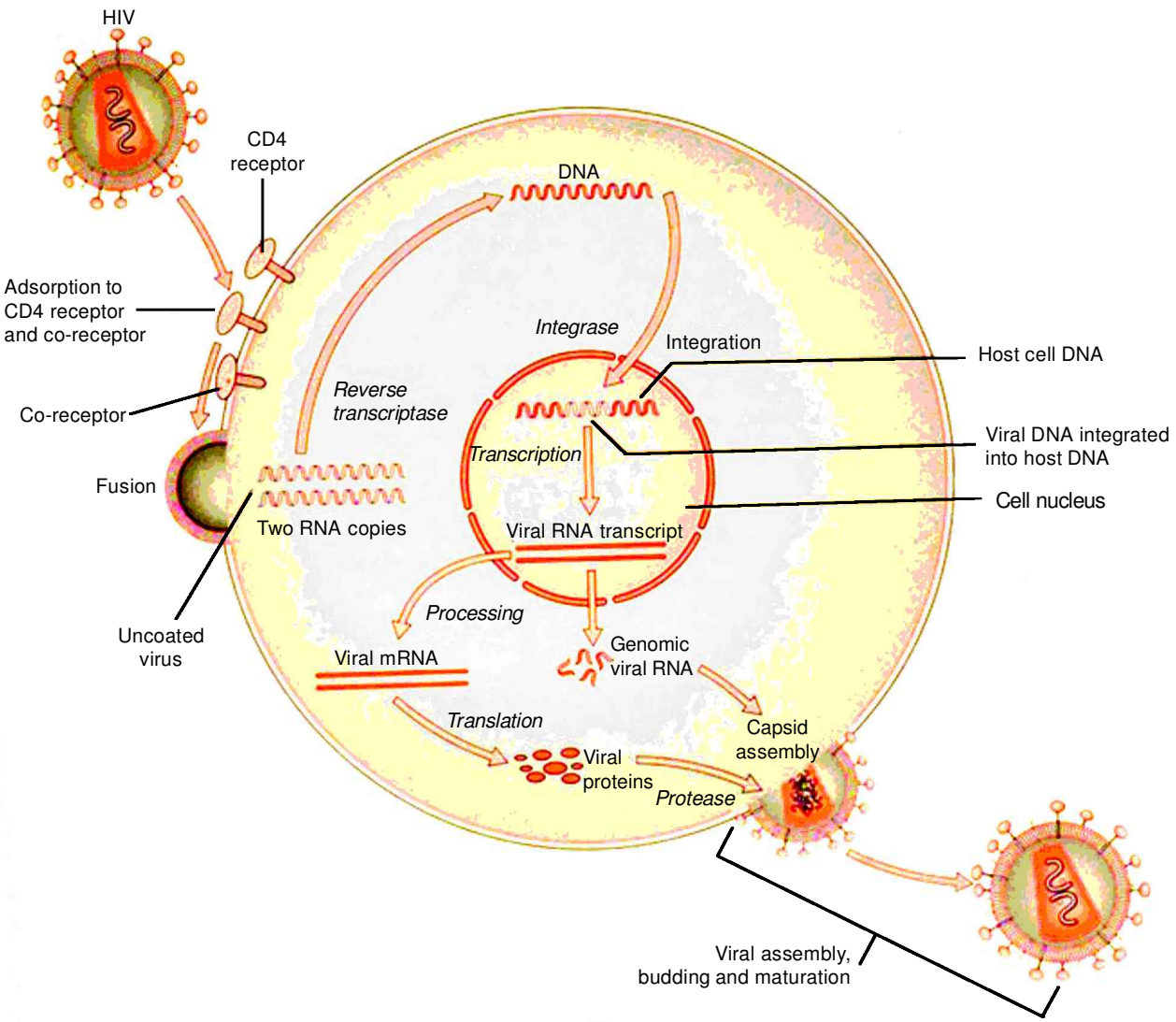

Fig 1. Life cycle of HIV and the sites of action of currently available antiretroviral drugs (reprinted from Ref 13, copyright 2002, with permission from Elsevier Science).

failure is, however, significantly higher in patients starting HAART with a CD4 cell count below 200 cells/μl.[12] BHIVA therefore recommends HAART in the asymptomatic individual before the CD4 count falls to below 200 cells/μl.

For up to 30% of patients in the UK, the question of when to start HAART is largely irrelevant as they present with a CD4 count already less than 200 cells/μl – highlighting the importance of early diagnosis, and emphasising that non-HIV specialists need to recognise the stigmata of HIV infection.

The aim of HAART is to improve the quantity and quality of life for the HIV-infected individual. This is achieved by increasing the CD4 count and reducing the viral load, ideally to below 50 copies/ml.[2]

Current antiretrovirals

Three classes of antiretroviral drugs are in routine use, targeting two enzymes (Fig 1, Tables 2 and 3): nucleoside (NRTI) and nucleotide (NtRTI) reverse transcriptase inhibitors, NNRTIs and PIs.

This list is not exhaustive as new agents are rapidly becoming available. New classes of drug are in development, including entry inhibitors and integrase inhibitors, that will target other parts of the HIV cycle. A patient's response to HAART mainly depends on the inherent potency of the regimen and on achieving adequate drug levels to inhibit the virus – which, in turn, is determined by resistance, toxicity, tolerability, pill burden, food restrictions and drug–drug interactions.[2] It is therefore important to individualise the regimen to achieve a patient's maximum response.

Drug toxicities (Table 4)

Drug toxicities can be both drug-specific and class-specific.

Mitochondrial toxicity

NRTIs and possibly NtRTIs inhibit mitochondrial DNA polymerase γ, impairing synthesis of the mitochondrial enzymes

Table 2. Currently recommended options for the antiretroviral-naïve individual.

Regimen	Recommendation	Advantages	Disadvantages
2NRTIs+NNRTI	Recommended	1 Equivalent or superior in surrogate marker trials compared with PI-based regimens at 104 weeks of follow-up 2 Easier	1 No RCT clinical end-point data 2 Shorter follow-up 3 Single mutations may lead to cross-class resistance
2NRTIs+PI*	Consider	1 RCT evidence with clinical end-points 2 Evidence of efficacy in late disease 3 Long-term follow-up	1 Toxicity common 2 High pill burden 3 Drug interactions
2NRTIs+2PIs**	Consider	1 Easier adherence 2 Better PK 3 Evidence of improved surrogate end-point efficacy for lopinavir/ritonavir compared with nelfinavir	1 No clinical end-point data 2 Possible increased toxicity and drug interactions
3 NRTIs	Consider for patients with low VL and adherence concerns	1 Spares PI and NNRTI classes 2 Fewer drug interactions 3 Low pill burden	1 No RCT clinical end-point data 2 Short-term surrogate marker data only 3 May be less effective at high viral loads

* Hard gel saquinavir should not be used as the sole PI. There are fewer data concerning use of soft gel saquinavir in this context than for other PIs.
** The primary reason for combining PIs is to improve pharmacokinetics. Suggested regimens include low-dose ritonavir with hard gel or soft gel saquinavir, lopinavir or indinavir.
NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetics; RCT = randomised controlled trial; VL = viral load.

Table 3. Currently licensed antiretrovirals.

NRTIs	NtRTI	NNRTIs	PIs
Zidovudine (AZT)	Tenofovir	Nevirapine	Saquinavir soft gel
Didanosine (DDI)		Efavirenz (DMP-266)	Saquinavir hard gel
Lamivudine (3TC)			Ritonavir
Stavudine (d4T)			Lopinavir
Abacavir			Amprenavir
Zalcitabine (ddC)			Nelfinavir
			Indinavir

NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; PI = protease inhibitor.

required for the production of adenosine triphosphate. The consequences of mitochondrial toxicity include myopathy, neuropathy, hepatic steatosis, peripheral neuropathy, pancreatitis and lactic acidaemia. The last two can be fatal if not detected early and should be suspected in any HIV-positive patient taking antiretroviral therapy who is unwell. Although lactic acidosis is rare, hyperlactataemia is more common; it often presents with mild constitutional symptoms or may be asymptomatic and of uncertain significance. Mitochondrial toxicity can occur at any time after the start of therapy but increases with duration of therapy and is not always reversible.

Lipodystrophy

Lipodystrophy is poorly understood in terms of aetiology, clinical features and management strategy. The features variously ascribed to the syndrome include peripheral fat loss (face, arms and legs), central fat accumulation (abdomen, breasts, dorsocervical spine) and lipomata. It tends to develop gradually over time and has been associated with the use of PIs and NRTIs, especially stavudine.[14] The body shape changes can have a stigmatising effect on an individual who may discontinue therapy as a result.

Hyperlipidaemia

Metabolic disturbances are often, but not always, associated with these body shape changes. They include hypercholesterolaemia, hypertriglyceridaemia, insulin resistance and glucose intolerance. The implications of these abnormalities and their association with cardiovascular risk have yet to be clearly established in the HIV setting, but there are anecdotal reports of premature cardiovascular disease. In many such cases there are additional risk factors for cardiovascular disease which should be addressed, and it is essential to consider P450 interactions when coprescribing.

Adherence

Less than 95% adherence to HAART has been associated with a significantly greater risk of virological and immunological failure, demonstrating that

greater adherence is needed than in other chronic medical conditions. Adherence is a complex human behaviour and may be affected by several factors:

- *patient factors:* health and medication beliefs, psychiatric morbidity, alcohol and drug use
- *provider factors:* doctor–patient relationship, adherence support devices/processes, and
- *regimen factors:* tolerability, toxicity, food restrictions, pill burden.[15]

Given the high degree of adherence required and the serious consequences of non-adherence, it may be wise for individuals to defer therapy until the above factors are optimal.

Antiretroviral resistance

Suboptimal adherence, absorption and potency of a regimen as well as drug interactions can lead to inadequate suppression of viral replication and the subsequent development of resistance mutations. These can confer resistance not only to one drug, but on occasion to other agents within a class or indeed to the whole class. This limits future treatment options and underlines the necessity of optimal timing for starting therapy for each individual. Resistant virus can in turn be transmitted to other individuals, and is being been increasingly frequently isolated from patients with primary HIV infection before treatment is started.[16] Measures to reduce virological failure and safer sexual practices to reduce HIV transmission are both required to minimise the risk of transmission of HIV resistant to HAART.

Patient discussion prior to commencing HAART

An open and honest dialogue between patient and healthcare professional is essential to help achieve optimal antiretroviral management. It should include the indications for treatment in this individual and the available drug options, including not only information on potency but also difficulties of adherence and toxicity/tolerability that may need to be faced. The clinician should aim to discuss, and take into account, the patient's beliefs and concerns about the necessity for treatment, including an assessment of the harm that may arise if treatment is not given at that time. Toxicity, pill burden, dosing frequency, the importance of adherence, food restrictions, drug interactions, and potential toxicities and their subsequent management should all be covered.

Table 4. Drug-specific toxicities of antiretroviral drugs.[2]

Antiretroviral drug	Major side effects
Nucleoside reverse transcriptase inhibitors	
Abacavir	Hypersensitivity in 4% – potentially fatal if rechallenge Non-specific symptoms: fever, rash, abdominal pain, respiratory symptoms
Non-nucleoside reverse transcriptase inhibitors	
Nevirapine	Severe rash (Stevens-Johnson syndrome), Fulminant hepatitis
Efavirenz	Central nervous system effects
Protease inhibitors	
Indinavir	Renal stones
	Crystalluria
	Interstitial nephritis
	Hyperbilirubinaemia

Conclusion

HAART has had a dramatic impact on the morbidity and mortality associated with HIV. The benefits of treatment however must be balanced against the emerging evidence on toxicities and the potential for drug resistance, particularly in view of the high levels of adherence required. An individualised approach towards when to start therapy and with which regimen is essential to optimise each patient's response and to harness the benefits it offers.

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Key Points

Highly active antiretroviral therapy (HAART) has had a dramatic impact on the morbidity and mortality associated with HIV

HAART is recommended in the asymptomatic patient prior to the CD4 count falling to below 200 cells/μl

Early diagnosis of HIV is important to allow a patient to commence HAART at the optimum time

The benefit of HAART must be weighed against the risks of drug toxicity, suboptimal adherence and virological failure

KEY WORDS: highly active antiretroviral therapy (HAART), HIV

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