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Current approaches to treatment for HIV-1 infection

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The last 3 years have seen a dramatic fall in mortality and morbidity from HIV infection. Four factors have contributed to this: an improved understanding of the pathogenesis of HIV infection; the availability of tests that could measure plasma viral burden; the development of new and more powerful drugs such as the protease and non-nucleoside reverse transcriptase inhibitors; and the completion of large clinical endpoint trials that conclusively demonstrated that potent antiretroviral combinations significantly delayed the progression of HIV disease and improved survival. Typical antiretroviral regimen now consist of at least three agents: one or two protease inhibitors or a non-nucleoside reverse transcriptase inhibitor combined with two nucleoside analogs. The goal of therapy is to reduce measurable plasma viral burden to undetectable levels. Viral load testing has made it possible to individualize therapy and to more accurately determine the best time to initiate or change therapy, long before declining $CD4^+$ counts would have given evidence of active viral replication. However, despite the impressive progress to date, there remain significant shortcomings with current treatment. Even with the most potent regimens available, there exists a proportion of patients (perhaps 20–50% of treated individuals) who fail to have complete and durable virologic responses to therapy. The shortcomings of current regimens are particularly evident in patients with high plasma HIV-1 RNA levels, extensive prior treatment, and advanced disease. Complexity, short- and long-term toxicities, cross-resistance, and drug-drug interactions all complicate current regimens. Viral resistance is increasingly encountered in clinical practice and transmission of resistant virus is well-documented. In addition, there remain concerns about the ability of the virus to evade current therapies, whether in viral reservoirs in non-lymphoid compartments or in lymphoid tissue, such as resting memory T cells. Thus there remains a need for new therapies as well as new strategies using existing drugs. *Journal of NeuroVirology* (2000) **6,** S8–S13.

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Introduction

One of the most dramatic advances in medicine in the latter part of the twentieth century has been the improved survival in patients with HIV infection who have had access to new potent antiretroviral therapies (Centers for Disease Control, 1997; Palella *et al*, 1998). This has created a situation where infection with HIV has changed from an inevitably fatal condition to a chronic disease that is potentially manageable over many years and even decades. It has also created a new challenge – management of infection with antiretroviral therapy in a way that maximizes the chances of long-term success, both virologic and clinical, while minimizing the potential for harm.

Several developments came together in the last few years to contribute the current state of therapeutics. These included technology that allowed more direct measurement of viral burden in specific sites, most notably the blood (Piatak *et al*, 1993; Saag *et al*, 1996); an improved understanding of the pathogenesis of HIV infection, most notably the realization that there were high levels of viral replication at all stages of infection and that progression correlated with rates of viral replication (Ho *et al*, 1995; Wei *et al*, 1995; Welles *et al*, 1996; Coombs *et al*, 1996; Mellors *et al*, 1997; Marschner *et al*, 1998) and the development of more potent

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inhibitors of viral replication, most notably inhibitors of HIV protease (Markowitz *et al*, 1995; Gulick *et al*, 1997). With the advent of potent therapy, it has been possible to show that inhibition of viral replication slows and even reverses immunodeficiency, with sustained elevations in CD4 lymphocyte counts and a gradual return towards normal immune function (Autran *et al*, 1997; Pakker *et al* 1998; Powderly *et al* 1998). There is clear clinical benefit, with decreased opportunistic infections and improved survival (Hammer *et al*, 1997; Cameron *et al*, 1998).

Furthermore, the effectiveness of therapy is closely linked to viral replication in that even relatively low levels of replication while on therapy, is associated with failure of that therapy usually with the emergence of resistant virus (Kuritzkes, 1996; Hirsch *et al*, 1998). At this point, the current aim of treatment from a virological perspective is to maintain viral replication below the limit of detection for as long as possible (Havlir and Richman, 1996).

Current antiretroviral therapy

Maintaining plasma viral loads at extremely low levels (below the limit of detection on sensitive assays has been associated with durable viral suppression and little evidence of viral evolution (Raboud *et al*, 1998). It appears that this is an achievable goal in many patients. Long term suppression of viral replication with a sustained rise in $CD4^+$ lymphocyte count can be achieved in 50–80% of newly treated patients with potent combination therapies (Gulick *et al*, 1997; Havlir *et al*, 1998; Staszewski *et al*, 1999). The effectiveness is less in some patient groups – notably those with advanced HIV disease, high levels of viral replication, and prior antiretroviral treatment (where resistance is likely to complicate therapy) (Wit *et al*, 1999).

In the United States, 15 agents in three classes have now been approved for the treatment of HIV infection (Table 1). Thus many choices of antiretroviral regimens are now available to clinicians, many of apparently comparable antiviral efficacy (Table 2). Although only protease inhibitor-based regimens have proven survival benefit, it seems probable that the important factor is the ability to control HIV replication, rather than the specific class of drugs by which it is controlled. Nonetheless choosing initial therapy is a complex process. There are clear differences in short term toxicity and complexity among the different regimens. In addition, long term differences are uncertain especially whether there are differences in clinical and immunological benefit. There are concerns about whether different regimens have different activities in potential 'sanctuary sites' especially the brain and the genital tract. Furthermore, initial choices may place constraints on future options because of resistance selection.

Indeed, there remains some controversy over the timing of initial therapy as well as the choice of initial regimen. Although most guidelines (USPHS, 1998; Carpenter *et al*, 1998) recommend that patients should be treated early in their infection (i.e., at high CD4 counts) with the most potent combination regimen, there is increasing awareness that such a blanket approach is not suitable for all patients. There is little disagreement that patients with AIDS or with rapidly progressive CD4 count loss or with very high viral loads should be treated aggressively. However, with the recognition that much of the immune damage is reversible with effective therapy, the imperative to treat all patients early in the infection has become less certain. Given that treatment is likely to require life-long adherence to complex multi-drug regimens that may have serious long-term toxicities, it is important to

Table 1 FDA-approved antiretroviral agents (mid-1999)

Nucleoside reverse transcriptase inhibitors	*Non-nucleoside reverse transcriptase inhibitors*	*Protease inhibitors*
Abacavir	Delavirdine	Amprenavir
Didanosine	Efavirenz	Indinavir
Lamivudine	Nevirapine	Nelfinavir
Stavudine		Ritonavir
Zalcitabine		Saquinavir
Zidovudine		

Table 2 Guideline for antiretroviral therapy*

Preferred (strong evidence of clinical benefit and sustained suppression)

Two effective nucleoside reverse transcriptase inhibitors (NRTIS)	*Potent protease inhibitor of NNRTI*
Zidovudine (ZDV)+ lamivudine (3TC)	Ritonavir
ZDV+didanosine (ddI)	Indinavir
Stavudine (d4T)+3TC	Nelfinavir
d4T+ddI	Saquinavir (soft gel)
ddI+3TC	Ritonavir+saquinavir
	Efavirenz

Alternatives (less evidence of ability to sustain HIV suppression):
2 NRTIs+nevirapine; 2 NRTIs+delavirdine; Abacavir+ZDV+3TC.
Not generally recommended:
2 NRTIs; 2 NRTIs+saquinavir (hard-gel capsule).
Contraindicated:
Monotherapy
Certain NRTI combinations:
D4T+ZDV; ddC+ddI; ddC+3TC; ddC+D4T.
*Adapted from Guidelines for the use of Antiretroviral Agents in HIV-Infected Adults and Adolescents. [US Health & Human Services, May 1999].

individualize therapy, balancing the long-term problems with current regimens with the potential for continuing viral evolution and progressive loss of immune function.

Problems with current regimens

The major issues facing physicians and patients with current treatments are the complexity of regimens which affects the ability to adhere to therapy, drug interactions which affect the ability to use concomitant medications, short-term and long-term toxicities which affect quality of life for patients, and viral resistance which affects subsequent options in therapy. All have to be considered when choosing antiretroviral therapy.

Adherence to therapy has emerged as an important issue in patient care. Many of the more potent regimens are extraordinarily complex, whether in terms of the number of pills patients need to take or the rigidity of timing of drug administration or the restriction in terms of food or other medications. Added to this are many gastrointestinal side-effects (especially nausea and diarrhea) which although minor in terms of threatening life, sufficiently interfere with daily living as to make adherence to the regimens difficult. As a result of all these factors, adherence is often poor (Mehta *et al*, 1997). However, unlike other chronic illnesses, such as hypertension, non-adherence or partial adherence to antiretroviral medications can have immediate biologic consequence, since it fosters the development of viral resistance (Hirsch *et al*, 1998; Wainberg and Friedland, 1998). There is now evidence that adherent patients have more prolonged or pronounced viral suppression when compared to non-adherent patients (Montaner *et al*, 1998).

The complexity of therapy complicates management in other ways – both the protease inhibitors and the non-nucleoside reverse transciptase inhibitors have complex interactions with the cytochrome P450 enzyme system – as substrates for and/or inhibitors or inducers of these enzymes, especially the CYP34A enzymes. This leads to issues in dosing the agents together as well as potential interactions with the many other drugs metabolized by this system (Barry *et al*, 1999). Additionally, long-term metabolic problems – including insulin resistance, diabetes mellitus, hyperlipidemias and abnormal fat distribution – are increasingly recognized (Carr *et al*, 1998; Yaresheski *et al*, 1999). In addition to the cosmetic and quality of life issues raised by such side-effects, they have also introduced the possibility of long-term cardiovascular complications that could result from antiviral treatment (Henry *et al*, 1998). Peripheral neuropathy, seen primarily with stavudine and didanosine is an additional side effect that greatly complicates effective treatment (Simpson and Tagliati, 1995).

Another potentially important issue is the possibility of viral 'sanctuary' sites. The variable penetration of drugs into different compartments of the body leads to the possibility that viral replication could continue although plasma viral replication is suppressed. The two leading candidates for such sanctuary sites are the central nervous system and the male genital tract. The central nervous system is particularly important because viral compartmentalization has been shown, with evolution of virus different to that seen in the periphery (Wong *et al*, 1997a). Many of the drugs used for treating HIV have low levels in the cerebrospinal fluid; however, the relevance of CSF levels to clinical effectiveness in the brain (or the relationship of CSF levels to brain tissue penetration) is unknown. However, viral resistance has been shown to develop at another anatomically privileged site (the testes) separate from the evolution of resistance in plasma (DePasquale *et al*, 1999). This suggests that careful study of the effectiveness of viral suppression in brain is an important research question. That said, there has not been to date clinical evidence of progressive HIV encephalopathy when viral replication is suppressed in the periphery; this fact suggests that, in most individuals, regimens that are effective in the plasma are likely to be effective elsewhere, including the central nervous system.

The final common pathway in drug failure (whatever its cause) has been the development of resistance (Hirsch *et al*, 1998). Resistant mutants may pre-exist and be selected in the presence of potent, but non-suppressive, treatment or they may emerge as a result of mutations occurring in the presence of drugs (Coffin, 1995). Resistance is important, not only because it leads to therapeutic failure of a regimen, but also because cross-resistance is common and, as a result, greatly compromises the effectiveness of subsequent regimens. A number of recent studies suggest that evaluating resistance using either genotypic or phenotypic assays for drug resistance can improve virologic responses, in the short-term (Durant *et al*, 1999; Baxter *et al*, 1999). However, although it is often possible to offer patients second regimens, subsequent 'salvage' regimens are typically associated with high failure rates (in terms of ability to suppress viral replication) (Deeks *et al*, 1999a). Although several investigators have described clinical stability in patients who are failing virologically (Deeks *et al*, 1999b; Ledergerber *et al*, 1999), such a situation is likely to be temporary and progressive immunodeficiency is likely to recur, unless viral replication is again controlled. A further consequence of the development of resistance is that there is evidence of transmission of resistant virus (including case-reports of transmission of multi-drug resistance) which has large public health implications (Hecht *et al*, 1998, Wainberg and Friedland, 1998).

Thus, one goal of therapy is to try to avoid resistance. Appropriate selection of both the timing and nature of initial therapy is probably the most important factor – to minimize the possibility of non-adherence. Other strategies worth considering include simplification of therapy or intensification. Simplification refers to the concept of starting with aggressive induction therapy, and after a period, simplifying treatment to a more manageable regimen. Although the initial tests of this approach proved unsuccessful (Havlir *et al*, 1998; Pialoux *et al*, 1998), more recent small studies that start with conventional protease-inhibitor based regimens, but substituting later with a non-nucleoside inhibitor have been encouraging (Martinez *et al*, 1999; Ruiz *et al*, 1999). This approach has the added potential benefit of minimizing the metabolic toxicities of the protease inhibitors. Intensification of therapy is based on the premise that it may be possible to identify patients at high risk of failing a conventional three-drug regimen and adding an additional agent, prior to the development of drug resistance. Trials to investigate such an approach are in progress.

Future options and challenges

One of the constraints to successful therapy has been the necessity that treatment is needed indefinitely; if one could eradicate viral infection then short term aggressive therapy might be more acceptable. Unfortunately, the identification of reservoirs, such as latent memory $CD4^+$ cells (Wong *et al*, 1997b; Chun *et al*, 1997; Finzi *et al*, 1997), where the virus can remain latent and where there is a very slow rate of viral decay (Finzi *et al*, 1999) makes eradication using antiviral therapy alone extraordinarily difficult (if not impossible). Although strategies to address this viral pool (such as targeted chemotherapy or activation of the memory cells with IL-2) are being investigated (Chun *et al*, 1999; Cooper and Emery, 1999), other strategies may be needed to address long term control of viral replication. Increasing attention is being turned to using the immune system as treatment. Drug holidays to trigger an immune response to active viral infection, as well as therapeutic vaccination given concurrently with potent antiretroviral treatment are also under study (Saag and Kilby, 1999).

There is also much attention being given to improvement of current antiretroviral therapy. Recognition of the constraints and difficulties associated with treatment have led to consideration of questions of timing of treatment. Studies are underway to determine the optimum initial therapy for HIV that will maximize both viral suppression as well as future options. In addition, many new drugs are in development. Most are in the current three classes of antiretroviral therapy, where development is being targeted to improve either pharmacokinetics or tolerability, although there is some interest also in activity of new agents against resistant virus. There is also much interest in new classes of antiretroviral therapy and agents that inhibit viral fusion show some promise in early clinical trials (Kilby *et al*, 1998).

In conclusion the current era of effective antiretroviral therapy has clearly led to prolongation of life in many patients with HIV infection, but has posed new challenges for clinicians and patients. Failure of antiretroviral therapy occurs frequently, and, although not always immediately associated with progression of immunodeficiency, is likely to signal a return to ultimate clinical failure and progression to AIDS, unless alternate treatment strategies are found. New agents not cross-resistant with existing agents, or agents targeting new viral mechanisms, are desperately needed to improve current options. Constraints to antiretroviral efficacy, such as viral reservoirs, resistance, adherence, drug interactions, and toxicities, can be managed, but they must be explored further to allow us to provide optimal individualized therapy. New approaches to salvage therapy and immune-based treatments must be rigorously evaluated. Finally given the difficulties that patients face with long-term indefinite treatment, clinical trials must determine the appropriate treatment strategy, i.e., whether treating early and hard is clinically advantageous to more conservative treatment approaches, such as waiting until there is clear (although not necessarily life-threatening) immune deficiency.

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