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Modern anti-HIV therapy[1]

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The Ten Commandments of antiviral treatment

Highly active antiretroviral therapies (HAART), usually consisting of two nucleoside reverse transcriptase inhibitors (NRTI) plus an HIV protease inhibitor (PI), have been widely used since 1996. They produce durable suppression of viral replication with undetectable plasma levels of HIV-RNA in more than half of patients. Immunity recovers, and morbidity and mortality fall by more than 80% [1, 2]. Treatment was thought to be particularly effective when started early; therefore, HAART was recommended for essentially all HIV-infected persons willing to commit themselves to lifelong therapy [3, 4].

Besides these successes, however, HAART also produces problems. HIV is not eradicated by present-day drugs, and patients often cannot comply with long-term combination treatment [5, 6]. Moreover, HAART causes unexpected and ill-understood side effects [7]. The dogma of earliest possible treatment has therefore come under attack.

Ten principles governing anti-retroviral treatment are summarised in Table 1. Starting and maintaining HAART is complex. Within the last few years, the numbers of antiretrovirals, their known and potential interactions with each other and with non-HIV drugs, and the list of their side effects have all increased exponentially. As a rule a physician specialising in HIV care should be consulted whenever HAART is started or changed. It is his task to ensure that the treatment chosen is optimal for the particular patient.

Keywords: anti-HIV therapy; HAART; protease inhibitor; reverse transcriptase inhibitors

Indications for starting treatment

Some have compared the course of HIV infection to a train speeding towards an accident. The CD4 count represents the distance from the locomotive to the site of the train wreck, while the viral load represents the speed [8].

The CD4 count indicates the degree of im-

1 This review is in full agreement with the recently published recommendations for antiretroviral HIV-treatment 2001 (see reference [10])

Table 1
10 principles for HAART.

1. Indication	The presence of HIV infection theoretically establishes the indication for treatment. Treatment does not usually start until sub-clinical immunodeficiency is apparent.
2. Combination	Antiretroviral treatment consists of at least three drugs.
3. First chance = best chance	The choice of drugs during a first treatment course determines what possibilities still remain when a second and different course of treatment becomes necessary later on. The chances of success are best first time round. Later on, alternatives are limited by selection of resistant mutants.
4. Complexity	Antiretroviral treatment is complex, in particular due to drug interactions and side effects.
5. Resistance	Selection of resistant quasispecies occurs frequently. Within substance classes, cross-resistance is complete among available NNRTIs, and partial among PIs and NRTIs.
6. Information	Starting and maintaining an effective anti-retroviral treatment is time-consuming, because the information needs of physician and patients are considerable.
7. Motivation and compliance	The patient's willingness to take the drugs regularly at prescribed times and dosages will largely determine the success of treatment. Patients must understand the relation between insufficient compliance and drug resistance.
8. Monitoring	The efficacy of antiretroviral treatment is established by regular measurement of viral RNA and CD4 counts.
9. Goals of treatment	The goal of treatment is durable suppression of viral RNA below 50 copies/ml of plasma. Such suppression minimises selection of resistant mutants, causes immune reconstitution and avoids morbidity and mortality.
10. Studies	Antiretroviral treatment continues to evolve towards greater simplicity and efficacy. Patients should be encouraged to participate in clinical studies aimed at optimising therapy.

munodeficiency and predicts short-term risk of opportunistic disease. Without treatment this risk is below 1% for the year to come when CD4 counts are above 500/µl, but rises to 30% with CD4 counts below 100. In the long term, prognosis is also determined by the viral load, i.e. the number of HIV RNA copies per ml of plasma. Elevated viral load predicts more rapid progression towards AIDS in population-based studies, although interindividual variations are enormous [9]. While HIV destroys CD4 cells and the lymph node architecture, causing progressive immunodeficiency, antiretroviral treatment suppresses viral replication, prevents further destruction of the immune system, and even allows for considerable repair in patients who start treatment while already immunosuppressed.

Treatment must be adapted to the individual patient, taking into account the speed of progression, acceptance of treatment by the patient, the likelihood of compliance, and possible side effects. The recommendations of Table 2 are only approximations because individual factors, though often decisive, do not lend themselves to abstractions in a table [10]. Possible advantages and disadvantages of an early start to treatment are outlined in Table 3.

Table 2
Indications for starting antiretroviral treatment.

Clinical stage	laboratory values	recommendations		
Acute HIV infection	irrelevant	consider HAART, obtain specialised consultation		
Chronic asymptomatic HIV infection (stage A)	CD4 count	viral load[1]		
		<10000	10000 to 50000	>50000
	>500	wait	wait	consider HAART
	350-500	wait	consider HAART	treat
	<350	treat	treat	treat
Symptomatic chronic HIV infection (CDC stage B or C)	irrelevant	treat		

[1]) using the Roche HIV Monitor® test

Table 3
Potential advantages and disadvantages of early antiretroviral treatment.

Possible advantages of starting treatment early	possible disadvantages of starting treatment early
Maximum suppression of viral replication; as a consequence, lower risk of selecting resistant mutants	risk of resistance as a consequence of suboptimal compliance
Prevention of immune deficiency and more complete immune reconstitution	duration of treatment efficacy may be limited
Less risk of side effects in patients whose general state of health is excellent	loss of quality of life through short-term side effects, and possible long-term toxicity
Healthy carriers are less contagious when treated: fewer new infections?	cost
	transmission of new infections with drug-resistant viruses

Choice of drugs (Table 4)

Three different classes of drug are currently available:

1. Nucleoside reverse transcriptase inhibitors (NRTI), such as abacavir (ABC), didanosine (ddI), lamivudine (3TC), stavudine (d4T), zalcitabine (ddC), and zidovudine (AZT).
2. Non-nucleoside reverse transcriptase inhibitors (NNRTI), such as efavirenz (EFV) and nevirapine (NVP)
3. Protease inhibitors (PI), such as amprenavir (APV), indinavir (IDV), lopinavir/ritonavir (LPV/r), nelfinavir (NFV), ritonavir (RTV), and saquinavir (SQV).

Optimal suppression of viral replication requires the use of at least three drugs, i.e. one or two NRTIs with one or two PIs, or with an NNRTI, or possibly three NRTIs. Choice of drugs is determined by several factors, including drug interactions, dosage intervals (e.g., by the need to accommodate professional activity), future therapeutic options, or possible pregnancy.

At present there are no clear criteria of choice between protease inhibitors and NNRTIs in initial treatment. Treatment experience with PIs is greater. Some advantages and disadvantages of the two drug classes are shown in Table 5.

The following treatment options are not recommended:

– Therapy with only one or two drugs.
– Combinations of ddI plus ddC, or ddC plus d4T (added toxicity), zidovudine plus d4T (antagonism), or ddC plus 3-TC (no data).
– Use of saquinavir, particularly the hard-gel capsule (Invirase®) without concomitant ritonavir (insufficient drug levels).
– Use of agenerase or saquinavir, without concomitant ritonavir, in combination with efavirenz (insufficient drug levels).

Treatment monitoring

Tolerance and side effects

NRTIs can be toxic to mitochondria, producing liver damage, lactic acidosis, lipoatrophy and polyneuropathy [11]. PIs cause nausea, vomiting and diarrhoea, elevate plasma cholesterol and triglycerides, induce insulin resistance and glucose intolerance and contribute, together with NRTIs, to the redistribution of fatty tissue: atrophy in the face and extremities contrasting with fat accumulation in breasts and abdomen [7]. Treatment of dyslipidaemia with statins is problematic because of the potential for drug interactions [12].

All drugs produce various specific side effects; an overview is presented in Table 6. Light shading means that the corresponding side effect has been reported in >5% of patients, black shading designates the drug's principal side effect. Because the drugs have usually been tested in combination, assignment of a particular side effect to a particular drug is often uncertain; this is particularly true of the various aspects of the lipodystrophy syndrome. Lipoatrophy and lactic acidosis seem to be more strongly associated with d4T than with other NRTIs, while fat accumulation may be particularly frequent when the combination of saquinavir and ritonavir is used [13].

The potential side effects necessitate regular patient visits. Our usual schedule requires a visit after 1, 2 and 4 weeks of treatment; if all goes well, the intervals may then lengthen to every two to

Table 4

Anti-HIV drugs available in Switzerland in 2001.

Generic name (abbreviation)	trade name	usual dosage in the absence of renal failure	class
Abacavir (ABC)	Ziagen®	300 mg bid	NRTI
Didanosine (ddI)	Videx®	400 mg qd*	NRTI
Lamivudine (3-TC)	3-TC®	150 mg bid	NRTI
Stavudine (d4T)	Zerit®	40 mg bid**	NRTI
Zalcitabine (ddC)	Hivid®	0,75 mg tid	NRTI
Zidovudine (AZT)	Retrovir®	250 mg bid	NRTI
AZT + 3-TC	Combivir®	1 tab bid	NRTI
AZT + 3-TC + ABC	Trizivir®	1 tab bid	NRTI
Efavirenz (EFV)	Stocrin®	600 mg qd	NNRTI
Nevirapine (NVP)	Viramune®	200 mg bid	NNRTI
Amprenavir (APV)	Agenerase®	1200 mg bid	PI
Indinavir (IDV)	Crixivan®	800 mg bid***	PI
lopinavir/ritonavir (LPV/r)	Kaletra®	400/100 mg bid****	PI
Nelfinavir (NFV)	Viracept®	1250 mg bid	PI
Ritonavir (RTV)	Norvir®	100 mg bid*****	PI
Saquinavir hard gel (SQVh)	Invirase®	400 mg bid***	PI
Saquinavir soft gel (SQVs)	Fortovase®	1200 mg tid	PI

NRTI = nucleoside reverse-transcriptase inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; PI = protease inhibitors

* 250–300 mg qd if weight <60 kg

** 30 mg bid if weight <60 kg

*** when co-administered with RTV

**** 533/133 mg bid (4 pills bid) when co-administered with efavirenz

***** 100 mg bid when co-administered with APV, IDV or SQVs; 400 mg bid when co-administered with SQVh

Table 5

PIs compared with NNRTIs in initial treatment when combined with NRTIs.

Drugs	advantages	disadvantages
Protease inhibitors	well documented clinical efficacy	heavy pill burden
	relatively slow selection for resistance when treatment is suboptimal	gastrointestinal side effects
	partial cross-resistance only; possible efficacy of a second PI in case of failure	elevation of serum cholesterol and triglycerides
		glucose intolerance
		lipodystrophy
		osteopenia?
Non-nucleosides	only a few pills to swallow	data concerning surrogate markers only
	better compliance	rapid development of resistance when treatment is suboptimal
	possibly less lipodystrophy	cross-resistance among currently used NNRTIs
		cutaneous side effects, including rare cases of Stevens-Johnson syndrome

Table 6

Frequent side effects of anti-HIV drugs.

	reverse transcriptase inhibitors								protease inhibitors					
	NRTIs						NNRTIs							
Clinical symptom	ABC	AZT	ddC	ddI	d4T	3TC	EFV	NVP	APV	IDV	LPV	NFV	RTV	SQV
Abdominal pain										▒				▒
Alterations of taste									▒				▒	
CNS symptoms							■							
Diarrhoea	▒		■						■	▒	■	■	■	■
Drug rash	■						■	■	■					
Fat accumulation							?	?	▒	▒	▒	▒	▒	▒
Fat loss	▒	▒	▒	▒	■	▒	?	?						
Fatigue		▒												
Fever	■							■						
Headaches		▒			▒	▒	▒	▒	▒	▒	▒		▒	▒
Hypersensitivity syndrome	■							■						
Kidney stones										■				
Myalgia		▒												
Nausea	▒	▒			▒	▒		▒	■	▒	▒	▒	■	▒
Pancreatitis				■										
Paraesthesias									▒				▒	
Polyneuropathy			■	▒	■									
Sleep disturbances	▒	▒				▒	■							
Stomatitis			▒											
Vertigo	▒						■						▒	
Vomiting	▒	▒							■	▒			▒	
Laboratory tests														
Amylase↑				▒										
Bilirubin↑										▒				
Cholesterol↑							▒		▒	▒	■	▒	■	▒
Creatinine↑										▒				
Cytopenias		■												
Glucose↑									▒	▒	▒	▒	▒	▒
GOT/GPT↑				▒	▒			■					▒	▒
Lactate↑	▒	▒	▒	▒	■	▒								
Macrocytosis		▒			▒									
Triglycerides↑									▒	▒	▒	▒	▒	▒

three months. For surveillance of toxicity we ask for a complete blood count, liver enzymes, lactates, and serum cholesterol and triglycerides.

Drug interactions

Protease inhibitors and NNRTIs are preferentially metabolised by cytochrome P3A. Thus there exists major potential for drug interactions. Drugs such as rifampicin or hypericum (St. John's wort) may lower PI and NNRTI concentrations by inducing cytochrome P3A. Other drugs may accumulate because they compete for cytochrome P3A with NNRTIs and PIs. This is the case, for instance, of ergot alkaloids (dramatic cases of ergotism with amputations have been published) and of many benzodiazepines [13, 14]. Hardly a week goes by without new interactions being reported; we recommend consulting internet resources for up-to-date information. Among the best of these sites are those produced by the Department of Pharmacology and Therapeutics of the University of Liverpool (www.hiv-druginteractions.org) and the electronic journal Medscape (http://medscape.com/home/topics/aids/aids.html).

Ritonavir deserves special mention. It is the most powerful inhibitor of cytochrome P3A known in medical therapeutics. Its capacity to inhibit metabolism of other PIs can be put to good use; increasingly, other PIs, such as indinavir, lopinavir, saquinavir, and amprenavir, are combined with small doses of ritonavir (100 mg twice daily) to boost plasma drug levels and lengthen intervals between doses [15].

Compliance

Compliance largely determines the long-term success or failure of HAART. The demands made upon compliance are greater than in most other diseases, because more than 95% of doses need to be taken correctly in order to ensure optimum re-

sults [6]. Patients must acquire adequate understanding of HIV pathogenesis, of the goals of HIV treatment and of pharmacokinetics. They should be able to recognise the most frequent side effects and know how to manage them [16].

Aids to improvement of compliance abound, although few have been tested rigorously. "Pill organisers", boxes containing all the drugs to be taken during one week in separate compartments, are popular. The establishment of a detailed written schedule, showing how and when to take the drugs in relation to meals and drinks, is recommended. More elaborate and expensive procedures involve use of electronic pill boxes, where a device records each time the bottle cap is unscrewed; the information can be downloaded into a computer and discussed with the patient. Directly observed therapy with once-a-day regimens is becoming a possibility; this may be particularly appropriate in combination with methadone maintenance.

Efficacy

Viral suppression as measured by lowering of the viral load, the rise in CD4 counts and clinical efficacy are all closely related. Above approximately 20 to 50 copies/ml, the nadir of viral load reached through treatment predicts the duration of viral suppression [17]. The time to optimal viral suppression depends on the initial viral load and on the sensitivity of the viral load test used [18].

Combination treatment must produce a rapid reduction in viral load, which should fall to below 400 copies/ml after twelve weeks and below 50 copies/ml after 24 weeks. Viral load measurements and CD4 counts are recommended every three months.

Resistance tests

Suboptimal treatment, lack of compliance, insufficient bioavailability or drug interactions can result in prolonged periods of low drug concentrations with continued viral replication and selection of resistant mutants. The presence of resistance genotypes and phenotypes can be detected by commercially available methods. Studies show that these tests are chiefly useful for excluding drugs to which the virus is resistant, but are less helpful in finding drugs to which the virus is sensitive [19–21]. Resistance tests are recommended in patients who are still untreated but have probably been infected since 1997, because they may harbour a primarily resistant HIV variant. They are also recommended after early treatment failure [22].

Measurement of plasma drug concentrations

In prospective studies, trough concentrations of protease inhibitors correlated well with the degree and duration of viral suppression [23]. However, the utility of these measures in clinical practice is not established. They are recommended in the event of unexpected toxicity, of suspected problems with compliance which cannot be investigated otherwise, or when multiple medication may produce unforeseeable pharmacokinetic interactions.

Treatment modification and simplification

Once a complicated drug regimen has suppressed viraemia, patients and physicians would like to simplify treatment. It is risky to replace triple therapy (with a PI and two NRTIs) by two drugs only [24, 25]. However, when the PI is replaced by an NNRTI, viral suppression persists for at least two years [26]. It is also possible to replace the PI/2NRTI combination with the three NRTIs ABC/AZT/3-TC, provided patients had been antiretroviral drug-naive when they started triple therapy [27]. Insulin resistance and serum cholesterol and triglycerides tend to normalise, but fat redistribution is usually irreversible. Strategic treatment interruptions are being evaluated in clinical trials but cannot yet be recommended in routine practice [28].

Procedures in case of failure

Treatment must often be changed because of intolerance, drug interactions or side effects. If viraemia is below 50 copies/ml, a single offending drug can be replaced.

The procedure is different in cases of virological failure, i.e. when viraemia does not fall below 50 copies/ml after 6 months (9 months if the initial viraemia exceeded 1 000 000 copies/ml [18]), or if viraemia rises to >200 copies after transient suppression. In this situation, a new combination should be chosen, containing if possible a drug from a class which has not been used previously. At least one additional drug should also be replaced by one to which the patient is unlikely to be resistant, on the basis of his/her drug history and resistance tests [10].

However, change to new therapy must never be automatic, especially in patients who have experienced long-standing failure on exposure to many drugs. Such patients often maintain CD4 counts at relatively high levels and are thus protected against clinical complications. On the other hand, salvage regimens may be ineffective and/or toxic, and drug holidays may produce falling CD4 counts [29]. Maintenance of a virologically failing regimen is therefore often the best option.

Start and finish of prophylaxis for opportunistic infections

Effective antiretroviral treatment, provided it is started in time, prevents immune deficiency and obviates the necessity of prophylaxis for opportunistic infections. Even if started late, HAART is usually followed by immune reconstitution. Prophylaxis for opportunistic infections can be discontinued after the CD4 count has remained above certain levels for at least three months. This level is 100 CD4 cells/µl for termination of prophylaxis for cytomegalovirus and non-tuberculous mycobacteria, and 200 CD4 cells/µl for ending of prophylaxis for *Pneumocystis carinii* pneumonia and toxoplasma encephalitis [30, 31].

Conclusions and outlook

Antiretroviral treatment has profoundly changed the prognosis of HIV infection. However, such treatment is complex. The chances of success are best in those who are previously untreated, and hence everything must be done to optimise the first treatment given. A specialised colleague should be consulted when starting or changing antiretroviral treatment.

Compliance remains essential for the success of treatment. All drugs must be taken as prescribed. In asymptomatic patients with CD4 counts above 350, better to refrain than to risk failure through insufficient treatment! It does not make sense to talk reluctant patients into accepting drugs; refusal of HAART must be respected.

Treatments continue to evolve. Triple therapy with two combination pills a day is already available. A once-a-day, one-pill protease inhibitor is in phase 3 trials. Drugs for new targets will follow. Within five years, judicious use of strategic treatment interruption, and of immune stimulation, may permit survival in good health and without drugs, at least for some patients.

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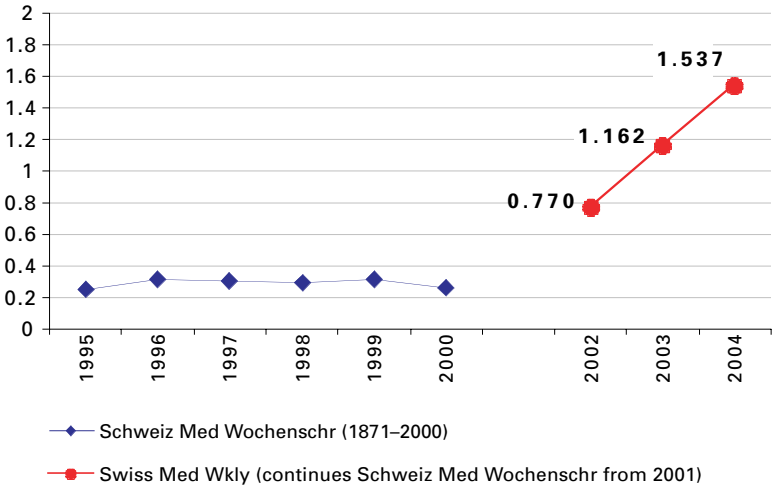

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