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REVIEW

Antiretroviral therapy in previously untreated adults infected with the human immunodeficiency virus type 1: established and potential determinants of virological outcome

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ABSTRACT

The aim of highly active antiretroviral therapy (HAART) for patients chronically infected with the human immunodeficiency virus type 1 is to achieve maximal and durable viral suppression. Maintaining the blood plasma HIV-1-RNA concentration (pVL) <50 copies/ml is currently considered appropriate for this goal. With the current treatment options, the percentage of previously untreated patients who achieve a pVL <50 copies/ml after one year of initial HAART is about 70%. Characteristics of the host, virus, drugs and the treatment team have been associated with the virological response to initial HAART. Adjusting the initial HAART regimen and patient management to a risk profile based on these factors is possibly helpful in improving the virological response to HAART. Adherence to a potent and well-tolerated HAART regimen is likely to be the most relevant factor for virological success. The additive value of the other factors needs to be clarified.

INTRODUCTION

The standard antiretroviral therapy (ART) first given to individuals infected with the human immunodeficiency virus type 1 (HIV-1) is highly active antiretroviral therapy (HAART). HAART is not well defined and is considered to consist of 'a combination of at least three selected antiretroviral drugs with good tolerability and efficacy'. The primary aim of initial ART is to achieve a maximal and durable viral suppression. Maintaining the blood plasma HIV-1-RNA concentration (plasma viral load, pVL) below a detection limit of 50 copies/ml is currently recommended to achieve this goal,[1-5] because it is associated with less virological failure than a level above 50 copies/ml and it may possibly prevent the emergence of drug resistance despite ongoing low-level (residual) viral replication.[6-12] If virological failure to the initial HAART regimen occurs, subsequent therapy is usually less effective due to accumulation of drug-resistance-associated mutations and cross-resistance amongst antiretroviral agents within the same class and generally the subsequent therapy is also more of a burden for the patient.[1,3,13-21] A good initial HAART regimen is therefore of great importance.

The aim of this review is to stress the importance of maximal and durable viral suppression, give an overview and update of the virological response to initial HAART and give insight into which factors have been associated with the virological response to initial HAART. Considering these factors could be of help in identifying patients with high and low risk for virological failure, and choosing an initial HAART regimen and the most appropriate moment to start therapy. To provide a better insight for physicians who are not familiar with antiretroviral therapy, a brief

historical overview and global perspective of ART is given. For this review PubMed and the Cochrane Library were searched. The search terms were "antiretroviral therapy", "highly active antiretroviral therapy", "HIV", "subtype", "clade", "HIV type 2", "pharmacogenetics" and "review". A criterion for selection was those articles which involved initial HAART. Also the reference list of articles selected in this way was screened and specific articles were added by the authors if they were not identified by the search strategy.

ANTIRETROVIRAL THERAPY IN HISTORICAL AND GLOBAL PERSPECTIVE

In June 1981, the world first became aware of the acquired immunodeficiency syndrome (AIDS).[22-24] Major scientific breakthroughs achieved during subsequent years are summarised in *table 1* and in *table 2* an overview is given of the antiretroviral drugs and their date of licensing by the USA Food and Drug Administration (FDA).[23-25] Now, in the year 2004, HIV can still not be cured with the available HAART regimens and there is still no preventive vaccine available.[26]

In countries where HAART could be widely applied, the HIV-1-related morbidity and mortality has decreased tremendously since its introduction in 1996 and the treatment has appeared to be cost-effective[15,27-33] Basis for clinical improvement is a lasting adequate virological suppression which leads to immunological recovery.[34-36] However, HAART is available to only a minority of the HIV-infected population and knowledge of its efficacy is based mainly on HIV-1 subtype M (major) subtype B. According to estimates of December 2003 about 40 million adults and children throughout the world are infected with HIV, of whom less than 2 million (<5%; those living in high-income countries) have access to HAART.[37] In the year 2000 it was estimated that HIV-1 subtype B accounted for only 12% of new HIV-1 infections.[38]

Thus, in contrast to current advances one must be aware that HAART is scarcely available in countries with limited resources, and that in these countries other HIV-1 subtypes are more prevalent. This may have therapeutic consequences, such as susceptibility to antiretroviral drugs, response to HAART, and rate and pattern of the emergence of drug resistance.[38-43]

WHAT IS THE VIROLOGICAL RESPONSE TO CURRENT HAART?

A HAART regimen is currently considered adequate when after three to six months a pVL of <50 copies/ml is achieved and this level of viral suppression is maintained.[1-3] In case of a baseline pVL >1,000,000 copies/ml it may take longer than six months to reach the concentration of <50 copies/ml.[44]
In *table 3* an overview is given of the virological response rates reported in published prospective studies in chronic

Table 1
Historical overview of antiretroviral therapy

1981	Recognition of first AIDS cases[22,188-192]
1983	Identification of HIV-1 as the cause of AIDS;[193-196] description of first AIDS cases in the Netherlands[197-201]
1985	FDA approval of first commercial blood screening test[202]
1986	Identification of HIV-2[203]
1987	Introduction of antiretroviral therapy: zidovudine[204]
1994	Reduction of HIV-1 transmission from mother to child[205-207]
1995	Availability of standardised (commercial) HIV-1-RNA assay,[208] which gave better understanding of HIV-1 viral dynamics[86,92,209-216]
1996	Release of first protease inhibitors and introduction of HAART[25,217-219]
1997	Ritonavir-induced pharmacokinetic enhancement of other PIs, which made twice-daily dosing of many PIs possible;[220-223] Recognition of a long-lived HIV cellular reservoir[224-233]
1998	After induction therapy maintenance with two NRTIs or one or two PIs or one NRTI and one PI is insufficient;[8,234,235] The virological response is more sustained when a blood plasma viral load nadir of 50 copies/ml is achieved;[6-12] First descriptions of the lipodystrophy syndrome;[236-242] Recognition of strong improvement of survival in HAART era[15,27-31]
1999	A high degree of drug adherence is needed to achieve a proper viral suppression;[151-156] Demonstration of residual replication during HAART, which made clear that treatment with the current kind of HAART would be for life[229-231]
2000	HAART can be relatively safely deferred until the CD4 count is nearing 200 cell/mm^3[4,31,50,60,61,243-246]
2001	Current guidelines to initiate HAART in HIV-1 infected adolescents and adults[1-3,62-64]

AIDS = acquired immunodeficiency syndrome, FDA = USA Food and Drug Administration, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, NRTI = nucleoside analogue reverse transcriptase inhibitor, PI = protease inhibitor.

Table 2
Licensed antiretroviral drugs and their date of approval by the Food and Drug Administration (FDA) of the USA[23-25]

CLASS AND GENERIC NAME	TRADE NAME	DATE OF FDA APPROVAL
Nucleoside-analogue reverse transcriptase inhibitor		
Zidovudine	Retrovir	19 March 1987
Didanosine	Videx	9 October 1991
Zalcitabine	Hivid	19 June 1992
Stavudine	Zerit	24 June 1994
Lamivudine	Epivir	17 November 1995
Zidovudine + lamivudine	Combivir	26 September 1997
Abacavir	Ziagen	17 December 1998
Didanosine (enteric coated)	Videx EC	31 October 2000
Zidovudine + lamivudine + abacavir	Trizivir	14 November 2000
Emtricitibine	Emtriva	2 July 2003
Nucleotide-analogue reverse transcriptase inhibitor		
Tenofovir	Viread	26 October 2001
Nonnucleoside reverse transcriptase inhibitor		
Nevirapine	Viramune	21 June 1996
Delavirdine	Rescriptor	4 April 1997
Efavirenz	Stocrin, Sustiva	17 September 1998
Protease inhibitor		
Saquinavir (hard gel capsule)	Invirase	6 December 1995
Ritonavir	Norvir	1 March 1996
Indinavir	Crixivan	13 March 1996
Nelfinavir	Viracept	14 March 1997
Saquinavir (soft gel capsule)	Fortovase	7 November 1997
Amprenavir	Agenerase	15 April 1999
Lopinavir + ritonavir	Kaletra	15 September 2000
Atazanavir	Reyataz	20 June 2003
Fosamprenavir	Lexiva	20 October 2003
Fusion inhibitor		
Enfuvirtide	Fuzeon	13 March 2003

HIV-1-infected, previously untreated adults and adolescents. The HAART regimens mostly used and studied are those of two nucleoside-analogue reverse transcriptase inhibitors (NRTIs) with either a (boosted) protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) or a third NRTI. As will be discussed later, the latter type of regimen is nowadays considered insufficient for initial ART. *Table 3* demonstrates that the studies with initial HAART are very heterogenous. This table and others[45,46] show that according to an 'intent-to-treat' analysis between 20%[47] and 88%[48] of patients achieve a pVL of <50 copies/ml at 48 weeks of therapy or later with an average of 50%. This may be about 70% with once-daily-dosed regimens and regimens with a low pill burden.[46,49] The 'intent-to-treat' analysis gives insight into the overall success of a certain HAART regimen.

It should be considered that in general clinical practice, the virological response rate to the first HAART regimen could be less than in prospective, randomised studies.[50] Also, as the knowledge and treatment possibilities evolves and patient management and therapy have improved (*tables 1* and *2*) there is a historical bias in the effectiveness figures of HAART regimens. One study showed that between 1996 and 1998 the rate of virological failure after one year of therapy decreased from about 50% to about 15% in an unselected population of an open clinic, but hereafter did not decrease further.[4] This decrease in virological failure could be related to increased experience and the introduction of boosting of PIs with low-dose ritonavir which resulted in a reduction of the dosing frequency and pill burden and an increase in plasma drug levels of PIs (*tables 1* and *2*).

Table 3
Overview of published prospective studies in which HAART is initially used

REF	RECRUITMENT PERIOD	FU	HAART REGIMEN	N	CD4	BASELINE VL	OT	ITT	% VL <50 C/ML +ΔCD4	REMARKS
[247]	7/'94-7/'96	52 w	AZT-3/DDI-2/NVP	51	395	17,732	ns	51 (<20 c)	139	
[47]	1/'95-5/'96	48 w	AZT-3/DDI-2/NVP	32	37.5	5.8 log	ns	37.5 (<400)*	101	*VL: NASBA
				ns	ns	<250,000	ns	45.5 (")*	ns	
				ns	ns	(250,000	ns	20.0 (")*	ns	
[78]	11/'95-4/'97	52 w	AZT-3/3TC/IDV	52	281	4.7 log	60	46 (<20 c)	178	
[248]	7/'96-12/'97	52 w	AZT-250/3TC/IDV	35	267	5.01 log	ns	66	168	
			D4T/3TC/IDV	34	313	5.21 log	ns	59	232	
			D4T/DDI-2,1/IDV	37	277	5.00 log	ns	48	166	
[79]	12/'96-1/'98	48 w	D4T/3TC/IDV	101	408	4.59 log	85	49*	142	*VL: RNA-pcr
			AZT-3,2/3TC/IDV	103	391	4.47 log	73	47*	110	<28 d AZT, DDI, D4T, DDC
[80]	12/'96-7/'97	48 w	D4T/DDI-2/IDV	102	422	31,623	70	41*	214	*VL: RNA-pcr
			AZT-3,2/3TC/IDV	103			69	35*	142	<4 w AZT, DDI, D4T, DDC
[9]	ns	48 w	AZT-3/3TC/NFV	99	284	231,884	83	ns (<400)	ns	
			AZT-3/3TC/NFV-500	97	307	308,075	56	ns (<400)	ns	
[48]	1-4/'97	52 w	D4T/3TC/RTV	33	640	35,481	ns	88 (<20 c)	131	
[69]	1-9/'97	48 w	AZT-2/3TC/EFV	154	350	60,256	90	64	201	3TC-, NNRTI-, PI-naive
			AZT-2/3TC/IDV	148	341	61,660	79	43	185	
			EFV/IDV	148	344	56,234	75	47	180	
[70]	2/'97-11/'98	48 w	AZT-2/3TC/APV-1200	116	442	4.61 log	79	34	128	
[81]	5/'97-10/'98	48 w	DDI-1/D4T/IDV	100	417	4.3 log	80.3	55.0	ns	
		96 w		100	417	4.3 log	79.0	44.0	238	
		48 w	DDI-1/D4T/NVP-1	89	394	4.3 log	80.7	53.9	ns	
		96 w		89	394	4.3 log	81.8	55.1	139	
		48 w	DDI-1/D4T/3TC	109	396	4.2 log	58.7	45.9	ns	
		96 w		109	396	4.2 log	50.9	28.4	233	
[249]	6/'97-10/'98	52 w	D4T/3TC-2/IDV	32	708	4.38 log	ns	84 (<200 c)	186	
							ns	72 (<5 c)	ns	
[82]	8/'97-6/'98	48 w	CBV/ABV/placebo	282	359	4.85 log	69	40	107	.
				180	ns	<100,000	57	45	ns	
				102	ns	>100,000	76	31	ns	
			CBV/IDV/placebo	280	360	4.82 log	82	46	93	
				176	ns	<100,000	74	46	ns	
				103	ns	>100,000	88	45	ns	
[250]	9/'97-12/'99	52 w	AZT-250/3TC/NVP	20	448	4.52 log	ns	73	172	
			D4T/3TC/IDV	22	398	4.62 log	ns	68	201	
			D4T/DDI-2/IDV	23	357	4.74 log	ns	80	190	

Table 3 continued

REF	RECRUITMENT PERIOD	FU	HAART REGIMEN	N	CD4	BASELINE VL	OT	ITT	% VL <50 C/ML +ΔCD4	REMARKS
[71,251]	11/'97-'98	52 w	D4T/DDI-1/NVP-2	60	415	4.59 log	67	ns	180	
			D4T/DDI-1/NVP-1	40	412	4.87 log	53	ns	ns	
[72]	11/'98-8/'99	12 m	CBV/NFV-2	70	351	65,806	79.2	65.2 (<20 c)	173	
				ns	ns	>100,000	ns	46.1 (<20 c)	ns	
			CBV/NVP	72	361	59,698	70.7	50.0 (<20 c)	162	
				ns	ns	>100,000	ns	57.1 (<20 c)	ns	
[101]	11/'98-7/'00	48 w	CBV/ABV	98	387	4.2 log	79	57	110	
			CBV/NFV-3	97	449	4.1 log	80	58	120	
[73]	ns	48 w	D4T/3TC/LPV-r	100	334	4.89 log	ns	78*	>213	*VL: bDNA. Different doses LPV-r
[252]	ns	204 w	D4T/3TC/LPV-r	100	338	4.89 log	97	70	440	Follow-up
[83]	1/'99-1/'01	48 w	ABV/D4T/DDI-1	60	190	5.0 log	ns	43 (<20)	140	
			AZT/3TC/SQV/RTV	60	152	5.0 log	ns	69 (<20)	140	SQV/RTV 400/400 b.i.d.
			AZT/3TC/NFV-2/NVP	60	144	5.1 log	ns	62 (<20)	185	
[253]	3-10/'99	48 w	D4T/3TC/KLT/Placebo	326	232	5.01 log	ns	67	207	
			D4T/3TC/NFV-3,2/Placebo	327	232	4.98 log	ns	52	195	
[74]	3-12/'99	48 w	DDI-1/D4T/NFV-3 } AZT-2/3TC/NFV-3 }	{ 511	411	4.69 log	ns	32	157	
					411	4.74 log	ns	32	189	
[254]	3/'99-1/'01	48 w	D4T/DDI-1/NVP-1	36	353	23,952	88	64*	119	*VL: bDNA
			D4T/DDI-1/EFV	31	416	22,789	100	74*	117	
[255]	11/'99-3/'00	12 m	DDI-1/3TC/EFV	40	164	5.4 log	ns	77	184	
[85]	ns	48 w	DDI-1/3TC-1/EFV	75	251	5.09 log	ns	77	208	
[49]	ns	52 w	DDI-1/3TC-1/EFV	34	184	5.21 log	88.9	77.4*	194	*VL: bDNA
			CBV/EFV	34	175	5.22 log	85.7	77.4*	183	
			CBV/NFV-2	34	169	5.16 log	60	50*	165	
[76]	02/'00-06/'01	48 w	D4T/3TC/NVP-1	220	200	4.7 log	ns	70	170	
			D4T/3TC/NVP-2	387	170	4.7 log	ns	65.4	160	
			D4T/3TC/EFV	400	190	4.7 log	ns	70	160	
			D4T/3TC/NVP-1/EFV	209	190	4.7 log	ns	62.7	150	
[256]	04/'00-10/'01	48 w	2NRTIs/IDV/RTV	40	80	230,957	74	50	167	IDV/RTV 400/100 mg b.i.d.
[103]	03/'01-11/'02	48 w	TZV/placebo	309	234	4.85 log	ns	61	174	
			CBV/ or TZV/EFV	765	242	4.86 log	ns	83	173	
[84]	ns	48 w	2-3NRTIs/IDV/RTV	57	50	308,000	96	40 (<80 c)*	149	*VL: NASBA
					42	<100,000	ns	40 (<80 c)*	ns	IDV/RTV 800/100 mg b.i.d
					15	>100,000	ns	38 (<80 c)*	ns	2 or 3 NRTIs

Table 3 continued

REF	RECRUITMENT PERIOD	FU	HAART REGIMEN	N	CD4	BASELINE VL	OT	ITT	% VL <50 C/ML +ΔCD4	REMARKS
[257]	ns	12 m	D4T/DDI-2/NVP	47	681	4.41 log	79 53	68 (<200 c) 45 (<5 c)	132 ns	
			D4T/DDI-1/NVP-1	47	700	4.34 log	85 46	73 (<200 c) 40 (<5 c)	154 ns	
[258,259]	ns	72 w	2NRTI's/IDV/RTV	93	195	210,000	94.6	59.5 (<80 c)*	265	*VL: NASBA IDV/RTV 400/400 mg b.i.d.
[260]	ns	48 w	DDI-1/D4T/ATZV-200	104	331	4.75 log	33	28	220	Phase II trial
			DDI-1/D4T/ATZV-400	103	357	4.65 log	42	36	221	
			DDI-1/D4T/ATZV-500	110	361	4.74 log	52	42	208	
			DDI-1/D4T/NFV-3	103	341	4.79 log	48	39	185	
[261]	ns	48 w	D4T/3TC/ATZV-400	181	294	4.74 log	40	35	234	Dose-finding study
			D4T/3TC/ATZV-600	195	302	4.73 log	41	36	243	
			D4T/3TC/NFV-2	91	283	4.73 log	39	34	211	

*REF = reference. FU = follow-up period in weeks (w) or months (m). N = number of patients included. CD4 = CD4+ cell count, preferentially the median. VL = viral load = blood plasma [HIV-1 RNA] copies/ml in log_{10} or linear count, preferentially the median. % VL <50 c/ml = Percentage with viral load <50 c/ml with reverse transcriptase PCR from Roche Pharmaceuticals. Between brackets VL is indicated if other limit of detection is used. OT = on treatment. ITT = intention to treat. +Δ CD4 = increase of CD4+ T-cell count from baseline. ns = not stated. * = other HIV-1 RNA assay, see remarks.*

ABV = abacavir 300 mg b.i.d. AZT-3 = zidovudine 200 mg t.i.d. AZT-2 = AZT 300 mg b.i.d. AZT-250 = AZT 250 mg b.i.d.

CBV = combivir (zidovudine/lamivudine 300/150 mg) b.i.d. DDI-2 = didanosine 200 or 125 mg b.i.d. DDI-1 = DDI 400 or 250 mg q.d.

D4T = stavudine 30 or 40 mg b.i.d. 3TC = lamivudine 150 mg b.i.d. 3TC-1 = 3TC 300 mg q.d. 2-3NRTIs = 2 or 3 nucleoside-analogue reverse transcriptase inhibitors.

TZV = trizivir (zidovudine/lamivudine/abacavir 300/150/300 mg) b.i.d.

EFV = efavirenz 600 mg q.d. NVP = nevirapine 200 mg b.i.d. NVP-1 = NVP 400 mg q.d. APV-1200 = amprenavir 1200 mg b.i.d.

ATZV-200, 400, 500, 600 = atazanavir 200 or 400 or 500 or 600 mg q.d. IDV = indinavir 800 mg q.d.. LPV-r = lopinavir-ritonavir b.i.d.

KLT = Kaletra(r) (lopinavir/ritonavir 400/100 mg) b.i.d. NFV-3 = nelfinavir 750 mg t.i.d. NFV-2 = NFV 1250 mg b.i.d. NFV-500 = NFV 500 mg t.i.d.

RTV = ritonavir 600 mg b.i.d.. SQV = saquinavir.

BASELINE CHARACTERISTICS THAT CAN INFLUENCE VIROLOGICAL RESPONSE

In ART-naive individuals with a chronic HIV-1 infection several factors present at baseline have been associated with the virological response to HAART. These factors can be classified as being related to the host (genetic make-up, adherence), the virus (drug-resistant virus, HIV-1 subtype), the drug, the treatment team or a combination of these. Some factors have been more extensively investigated because they are more easily available, for example the CD4 count, pVL, blood plasma drug levels and patient adherence. The impact of these determinants on virological response is more clear and established. On the other hand, HIV pharmacogenetics, which can elucidate factors at baseline that are associated with proper drug concentrations, toxicity and virological response, is still in its infancy.[51-58] Next, we will describe the factors associated with the virological response to initial HAART starting with the two most extensively investigated factors.

Low $CD4^+$ T lymphocyte cell count

A low $CD4^+$ T lymphocyte cell count (CD4 count) is usually associated with a high pVL. This makes it unclear which of these two is mostly associated with the virological response. Retrospective cohort studies have shown that patients with a baseline CD4 count <200 cells/mm^3 have a worse virological response and more progression to HIV-related morbidity than patients with a higher baseline CD4 count.[4,31,50,59,60] The question is whether this difference in response is due to a difference in biology (host-virus-drug interactions) or in behaviour, for example that patients with a low CD4 count are probably more difficult to treat (initially). Deferring initial HAART until the CD4 count is between 200 and 350 cells/mm^3 is associated with a minimally increased risk of AIDS compared with starting at a CD4 count >350 cells/mm^3, depending on the pVL, as the risk of AIDS is higher when the pVL is higher.[4,31,50,60,61] As a result, since 2001 most guidelines advise adolescents and adults with a chronic HIV-1 infection to start HAART when their CD4 count is nearing 200 cells/mm^3 [1-3,62-64] in order to postpone possible long-term side effects of HAART, such as lipodystrophy syndrome and cardiovascular diseases.[65-68]

High blood plasma viral load

For ART consisting of two NRTIs and either a (boosted) PI or an NNRTI, there is conflicting evidence from studies (*table 3*) as to whether the risk of virological failure is increased[9,47,49,69-77] or not[49,69,72,78-85] if the pVL at baseline is high. On theoretical grounds there could be an increased risk of virological failure when the pVL is very high. The virological response after HAART is initiated in ART-naive patients biphasic with a rapid decay of the pVL in the first two weeks and a slower decay thereafter. Given that there is a constant first- and second-phase viral decay rate after initiation of HAART, more time is required to reach the level of <50 copies/ml with a higher baseline pVL,[44,71,73,85] thus increasing the window for early development of drug resistance.[4,86-90] It is estimated that per HIV-1 replication cycle one to two base-pair transcriptional errors occur.[19,91,92] Thus, there could be an increased risk of an (early) emergence of strains with one or more drug-resistance mutations if the pVL at baseline is high, especially when drugs with a low genetic resistance barrier (drugs for which only one or two specific mutations in the reverse transcriptase or protease gene are needed to cause significant resistance), such as lamivudine, atazanavir, nelfinavir and the NNRTIs, are components of a triple-drug regimen.[90,93,94]
Adding a fourth active drug in the initial phase of therapy if the pVL is high (e.g. >300,000 copies/ml) is defendable and some guidelines do recommend this strategy.[64]
A triple-class, five-drug regimen (three NRTIs, a (boosted) PI and an NNRTI) is more potent than a two-class, three-drug regimen (two NRTIs and a PI), thus giving rise to the question as to what the optimum potency of a HAART regimen should be.[95-97] However, more drugs implicates more toxicity. An alternative is to use three drugs with a high genetic resistance barrier in the initial phase.

It has now become obvious that when the baseline pVL is high, (certain) convergent regimens consisting of three NRTIs as initial therapy are virologically inferior to divergent regimens consisting of two NRTIs and either a (boosted) PI or NNRTI (*table 3*).[1,3,81-83,98-101] Possibly this inferiority is also the case at low pVL. Some studies, such as a study with tenofovir, lamivudine and abacavir once daily as initial therapy,[93] a study with zidovudine, lamivudine and abacavir,[102,103] and a study with didanosine, lamivudine and tenofovir[94] were even prematurely aborted because of more virological failure. In one very small study with subjects with sustained control of pVL there was more viral evolution in the lymph nodes with subsequent development of drug resistance mutations in the subjects who were treated with dual or triple NRTIs alone compared with the divergent regimens.[104] What needs to be clarified is whether switching to a triple NRTI regimen during proper virological suppression in the absence of previous suboptimal treatment or resistance is associated with more virological failure or not[99,100,105-107] and whether these convergent NRTI regimens can still be applied when the baseline pVL is (very) low.

Early virological response

It has been demonstrated that the first phase pVL decay rate after initiation of HAART might be predictive for the potency of the regimen and the virological response at two to three months.[108,109] Similarly a decrease in pVL by 1 $\log_{10}$

at week 4 or a pVL of <500 copies/ml at week 4 or 8 of therapy has been associated with a more favourable virological response at 24 or 48 weeks of therapy.[9,110]

Primary infection with drug-resistant virus

Of great concern for virological response to initial HAART is the presence of (archived) drug-resistant virus at baseline.[111,112] The prevalence of HIV-1 viruses with one or more RT and/or protease resistance-associated mutations in recently infected individuals has increased in some parts of the world to 20%.[111,113-117] In Europe this is about 10%.[118,119] Thus, depending on the local prevalence, initial HAART needs to be optimised based on empiricism or on genotypic resistance testing. The International AIDS Society – USA Panel recommends a baseline drug resistance test for an HIV-1 infection that was acquired less than two years previously in areas with a drug resistance prevalence of more than 5%.[120]

SI and NSI phenotype of the virus

In the early asymptomatic phase of HIV-1 infection nonsyncytium-inducing (NSI) (macrophage or CCR5-tropic) virus variants predominate. In the later course of the infection syncytium-inducing (SI) (T-cell or CXCR4-tropic) variants emerge. This switch in phenotype predominance coincides with a faster progression of the infection.[121,122] *in vitro*, zidovudine preferentially inhibits NSI variants, while didanosine preferentially inhibits SI variants.[123,124] For lamivudine and the protease inhibitor ritonavir an equal inhibition of NSI and SI variants was observed.[122,123] For the other NRTIs and the NNRTIs the effect on NSI and SI has not been compared. The difference in inhibition of NSI and SI variants by zidovudine and didanosine is probably due to differences in intracellular phosphorylation to the active triphosphate.[122,123] Zidovudine and stavudine are preferentially phosphorylated in activated cells, while didanosine, lamivudine and zalcitabine are preferentially phosphorylated in resting cells.[125-127] Activated CD4+ cells express more CCR5 receptors and resting cells express more CXCR4, thus giving a rationale for the divergent inhibition of NSI and SI variants by zidovudine or stavudine and didanosine or lamivudine or zalcitabine, respectively.[122,123] This difference in inhibition is probably of no importance when current HAART is applied, but may be relevant for the use of CCR5 blockers.[128,129]

HIV-1 subtype

Based on genetic divergence in the env, gag and pol region, HIV-1 is phylogenetically divided into an M (major), O (outlier) or N (non-M, non-O or new) subtype or clade.[38,39,41] These three subtypes are further subdivided into several subtypes or clades. The O and N subtypes are rare and mainly restricted to West Africa.[41] The M subtype accounts for >90% of reported HIV/AIDS cases.[39] M subtypes that have been identified until now are A, B, C, D, F, G, H, J, K, AE and other recombinants, called circulating recombinant forms (CRFs).[38,39,41] In Europe, the Americas, Australia and New Zealand subtype B is the most prevalent, while the non-B subtypes are mainly prevalent in the other continents. However, due to travel and migration within the Western world these differences in prevalence are changing.[41,130-133]

Within the M subtype inter-clade variation in env is 20 to 30%, in pol about 10% and in gag much less than 10%.[38,39,134] The pol gene encodes for reverse transcriptase, RNase, protease and integrase. These inter-clade variations are or can be accompanied by differences in biological behaviour, susceptibility to antiretroviral drugs, response to HAART, and rate and pattern of emergence of drug resistance.[38,39,41-43] Parallel to this, the HIV-1 subtype outlier is naturally resistant to NNRTIs due to different amino acids at RT position 181.[39,41] Also, HIV-2 is naturally resistant to the NNRTIs because in the wild-type virus amino acid substitutions associated with drug-resistance mutations in HIV-1 (at position 181, 188 and 190) are already present. Furthermore, there is a faster emergence of the multi-NRTI-resistance mutation Q151M and a rapid emergence of genotypic drug resistance (D30N) to the PI nelfinavir in HIV-2.[38,39,135-139]

Clinical studies with antiretroviral therapy have predominantly been done in populations with the B subtype (*table 3*). Prospective studies comparing the virological response among HIV-1 subtypes are lacking. Three retrospective studies with a limited number of patients showed no difference in response to HAART between B and non-B subtypes.[140-142] Thus, the impact of the different HIV-1 M subtypes on the virological response to initial HAART needs to be established.

Trough concentration of PIs and NNRTIs in blood plasma and the intracellular concentration of triphosphorylated NRTIs

Retrospective and prospective studies have shown a correlation between the blood plasma (trough drug concentration of PIs and NNRTIs and the virological response.[17,143-147] Minimally effective drug concentrations have been defined, and nowadays therapeutic drug monitoring, the proactive regular measurement of drug concentrations, is considered a standard during PI and NNRTI treatment in some countries.[1,3,143-145,148] Likewise, a positive association was found between the intracellular concentration of triphosphorylated NRTIs and the virological response.[149,150]

Adherence to therapy

Proper adherence to the dosing interval and administration requirements of the drugs is one of the most important

factors for a durable virological success. Adherence to therapy of at least 90 to 95% is needed with HIV-1 to properly suppress the virus for a prolonged time.[151-156] Factors that influence adherence to therapy are dosing frequency,[157,158] pill burden,[45,49] acute and long-term toxicity of the drugs,[16,159-161] and sociocultural factors.[162] Before initiating HAART it is essential that the patient is willing and cooperative in taking the drugs and that he/she is well informed, instructed and aware of the drug intake requirements, adverse effects and consequence of nonadherence.

Frequent consultations and monitoring of drug levels, pVL and adherence in the early phase of therapy might be useful for this purpose.

Pharmacodynamic interaction between antiretroviral drugs
Stavudine and zidovudine have a proven antagonistic effect.[3,163,164] The cause of this antagonism is unclear, but theoretically it could be due to steric hindrance at the enzyme active site or due to interference in the metabolic pathway of the drug. The virological inferiority of a regimen consisting of only three NRTIs could also be due to antagonism or a low genetic barrier to resistance.[93,94] On the other hand, genotypic resistance to lamivudine (mutation M184V) can (partially) reverse resistance to zidovudine and improve the virological response to tenofovir.[19,165] Possibly, resistance to NRTIs causes (*in vitro*) hypersusceptibility to NNRTIs and *vice versa*.[20,166-171] Another example of increased susceptibility that can occur is the presence of the N88S protease gene mutation and improved virological response to amprenavir.[172] Whether such *in vitro* hypersusceptibilities result in clinical benefit remains to be proven.[171]

Genetic make-up of the patient
Certain polymorphisms of chemokines (SDF-1 3'a, G protein b3 subunit 825T), chemokine receptors (CCR5-delta32, CCR2-V64I, CCR5-promotor allele 59029-G), and certain HLA alleles (B57, B27, Bw4, B*5701, B14, C8) are associated with a slower progression of the HIV-1 infection, while CCR5-promotor allele 59029-A and other HLA alleles (B35, Cw4, DQB1*0402) are associated with a faster progression of the infection.[57,58,173-178] Some of these factors are associated with a better (CCR5-delta32) or worse (the combination of wild-type CCR5, wild-type CCR2 and homozygous CCR5-promotor allele 59029-A) response to ART.[53,56-58] Also, a homozygous C/C genotype at base-pair position 3435 in exon 26 of the multidrug resistance transporter 1 (MDR1) gene is associated with a worse virological response to HAART compared with the T/T or C/T genotype.[54,55,57,58,179]

This may have consequences for choosing the type of initial HAART to be used among ethnic groups since the C/C genotype is more prevalent in Afro-Americans and Africans than in Caucasians and Asians.[57,58,180-183]

Experience and knowledge of the treating physician
A better survival was associated with more experience in treating HIV on the part of the physician as well as better adherence to therapy by the patient.[184] These two factors even outweighed the worse outcome if HAART was started at a CD4 count below 50 cells/mm^3.[184] Although not evaluated, the improved outcome was probably partly due to a better virological response because of a better instruction and management of the patient by the more experienced physician.

EPILOGUE

The aim of initial HAART is to achieve maximal and durable viral suppression which is currently a pVL of <50 copies/ml. With current knowledge, patient management and treatment possibilities virological success after one year of initial HAART has improved to about 70%. So, there is much room for further improvement and the challenge is how to achieve this. Adjusting therapy to a virological failure risk profile could be a useful strategy. As an example, a patient with a high pVL (e.g. >300,000 copies/ml), a low CD4 count (e.g. <100 cells/mm^3) and a low socioeconomic status (e.g. poor housing) could be given a four-drug divergent regimen as initial HAART or a three-drug divergent regimen with a high genetic barrier to resistance, and such a patient should be more intensively monitored.
How the clinical relevance of the several determinants of virological response compare with each other needs to be established. However, likely adherence to a potent and well-tolerated HAART regimen is the most basic and relevant factor for virological success and the other factors probably modulate this response.

SUGGESTIONS FOR FURTHER STUDIES

What needs to be further evaluated is the importance of other factors, what are early markers for long-term virological response, whether switch to a triple NRTI regimen is virologically safe, whether once-daily-dosed regimens have a virological advantage over twice-daily-dosed regimens, how regimens with a low, middle and high genetic resistance barrier compare with each other, how the virological response in non-B subtypes compare with subtype B, and what level of virus suppression is needed to prohibit virological failure. As long as HIV cannot be cured, this last factor will really define what should be considered as HAART. However, improving adherence to therapy is likely to be the most relevant measure to achieve a durable virological success.[185]
Since the risk of HIV-related morbidity and mortality is

substantially increased as long as the CD4 count is below 200 cells/mm^3, strategies to raise the CD4 count more rapidly above this threshold (e.g. type of HAART regimen, interleukin-2) should also be explored.[186] Chronic hyperactivation of the immune system might be an important cause of CD4 cell loss.[187] Considering the toxicity of HAART and the importance of a high level of adherence to HAART, it is also worthwhile to evaluate inhibition of this hyperactivation.

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