

# Treatment Strategy Issues for Chronic HIV-1 Infection in Adults: The Dilemma of Life-long Antiretroviral Treatment

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**Abstract:** Highly active antiretroviral therapy regimens (usually three-drug combinations) have shown undisputable efficacy in the reduction of the morbidity and mortality of HIV-infected patients. However, these regimens are only virustatic, which means that, in order to suppress viral replication, treatments should be maintained for life, without any additional benefit over time once immune restoration has been obtained. Besides, there is a debate on when to start therapy because profound immunodepression may not be totally reversible, recognizing that earlier treatment means longer drug exposure. On the other hand, the long-term toxicity of these drugs has generated new problems such as the appearance of the lipodystrophy syndrome and the increase of cardiovascular morbidity observed in patients treated for several years, particularly with HIV protease inhibitor-containing regimens. Therefore, new drugs are needed, not only for patients experiencing virological failure but also for successfully treated patients, in order to reduce toxicity, and these new drugs must now be screened for metabolic disturbances and adipocyte toxicity as well as for antiretroviral activity. Alternatively, new strategies, such as specific or non-specific immune-based therapy, reinforcing drug efficacy or allowing treatment interruptions, must be developed.

## INTRODUCTION

There is no doubt that the introduction of highly active antiretroviral therapy (HAART) regimens in 1996, has dramatically changed the prognosis of patients infected with the human immunodeficiency virus (HIV) in industrialised countries. Large observational studies have clearly documented the fall of the incidence of deaths, opportunistic infections and of the need for hospitalisations [1,2]. This effect on mortality and morbidity is sustained, as shown by a recent study documenting a continuing decrease in the « late-HAART » period (1998-2002) [3]. However, it should always be remembered that antiretroviral drugs, even given in association, are only virustatic and that, even in patients with undetectable plasma HIV RNA loads, low-grade replication still occurs [4]. In other words, the goal of eradicating the infection does not appear realistic at the present time.

As a consequence, HIV infection is now envisioned as a chronic disease necessitating continuous, possibly life-long treatment. This generates new concerns, knowing the short-, mid- and, above all, long-term toxicity of drugs. The most crucial example is the indication that exposure to HAART increases the risk of cardiovascular events, as discussed below. Another concern could be the increase of non AIDS-defining cancers (lung cancers) [5,6], although this is probably not an effect of antiretroviral drugs *per se*, but rather a result of prolonged life expectancy and exposure to cancerogenic factors.

In summary, the indisputable benefits of HAART must be balanced against its limitations and its potential deleterious effects in the long-term, both of which are now more clearly measured. This review addresses some of these issues for adult patients and underlines the need for innovative strategies in order to resolve this uncomfortable situation.

## BENEFITS OF HAART

### Immune Restoration

In most patients, HAART allows a dramatic fall in HIV replication, as reflected by the reduction of the HIV RNA plasma load, which most frequently reaches undetectable levels. Subsequently, the disappearance of direct and indirect effects of HIV on the immune system allows for immune restoration, reflected by the increase of the blood CD4 cell count. Although the immunopathogenesis of HIV infection, and, as a consequence, the mechanisms of immune restoration on HAART are not fully understood yet, one can accept the following scheme. Immune restoration is biphasic, with a first, rapid increase of memory CD4 cells resulting from redistribution from lymphoid tissue and inflammatory sites, and a second, slower increase of naive CD4 cells, in which thymopoiesis certainly plays an important role [7, 8].

The quantitative and kinetic aspects of immune restoration seem to depend on a number of host factors : Younger age favours the speed and intensity of CD4 recovery, probably in relation with preserved thymic function [9, 10], while hepatitis C virus coinfection seems to hinder CD4 recovery [11]. Although this is debated, it has been suggested that immune recovery on HAART depends on which regimen has been prescribed [12,13]. Specifically,

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protease inhibitors may have a favourable effect on the CD4 count, independent of their action on viral replication, possibly by preventing CD4 cell apoptosis [14].

CD4 cell recovery is efficient, as demonstrated by studies showing the restoration of *in vitro* T cell responses to recall antigens and opportunistic agents [15,16]. The profoundly disrupted T cell repertoire of untreated patients also tends to improve under the effects of treatment, even if it does not seem to return to normal [17]. However, the best index of efficient immune recovery on HAART is the demonstration that primary and secondary prophylactic treatments for opportunistic infections can be safely interrupted in patients reaching a CD4 count greater than 200/ $\mu$ L, as shown in several open and controlled studies [18-24].

The question of whether specific immunity to HIV can also be recovered is still open. However, recent reports indicate that T cell anti-HIV immunity can be recovered in patients who either started HAART at relatively high CD4 counts, or who had been treated for a long time [25-27]. This may be an interesting indication that duration of treatment could compensate for later initiation, at least for some aspects of immune restoration. In any case, this issue is relevant to the future development of specific immunotherapy (therapeutic vaccines), and possibly, programmed treatment interruption.

It must also be recalled that immune restoration in itself can be responsible for unwanted effects, although this is certainly marginal in regard to the overall benefit. First, the paradoxical exacerbation of pre-existing infectious diseases due to intracellular pathogens has been reported [7,28]. The recovered possibility to mount an immune specific response and an inflammatory response is responsible for the aggravation that has been described in infections with mycobacteria and viruses. Second, thyroid autoimmunity (Graves' disease) has been described in severely immunocompromised patients recovering relatively high CD4 cell counts [29], which may, interestingly, reflect

qualitative abnormalities of T-cell repertoire reconstitution in a small number of patients.

In summary, HAART is responsible for an efficient immune restoration, which represents the ultimate goal of therapy, since the development of opportunistic diseases is directly dependent on immune impairment, and not on HIV replication. However, all the correlates of immune restoration, and of its completeness, if such a goal is achievable, are not precisely known.

#### WHEN IS HAART MOST BENEFICIAL?

Recently published cohort studies have underscored several facts that have been influential in making the current recommendations in Europe and in the USA on when to start antiretroviral therapy. First, the CD4 count has the strongest prognostic value in the short and mid term (as opposed to the longer term prognostic value of HIV RNA load). Second, immune recovery is observed whatever the baseline CD4 count, although the time to reach a « safe » value is longer in the most immunocompromised patients, leaving room for a period when patients remain at risk for opportunistic diseases. Third, the rates of virological success and failure of HAART appear independent of baseline CD4 and plasma RNA levels [30,31]. Finally, the development of metabolic toxic effects of drugs depends on the length of exposure.

As a logical consequence, current recommendations are to initiate antiretroviral therapy in all symptomatic patients, and in all patients with a CD4 count lesser than 200/ $\mu$ L. Asymptomatic patients with a CD4 count lesser than 350/ $\mu$ L can be considered for treatment, particularly when the plasma HIV RNA load is high, but in asymptomatic patients with more than 350/ $\mu$ L, treatment initiation is generally not recommended by French and US experts [32-34], which is different from the attitude proposed by the European AIDS Clinical Society Euroguidelines Group [33] (Table 1). However, for asymptomatic patients with a CD4 count between 200 and 350/ $\mu$ L and a plasma HIV RNA load >

**Table 1. Current Recommendations for Initiating Antiretroviral Treatment in Adults (Viral Load Expressed as HIV1 RNA Copies per ml of Plasma)**

Patient category	US recommendations [32]	EACSEG* recommendations [33]	French recommendations [34]
Symptomatic, any CD4	Treat	Treat	Treat
Asymptomatic, CD4 < 200/ $\mu$ l	Treat	Treat	Treat
Asymptomatic, 200/ $\mu$ l < CD4 < 350/ $\mu$ l	Consider treatment or closer monitoring if viral load > 55,000	Treat	Treat on the basis of: -Patient's preparation -CD4 decrease slope -Value of viral load
Asymptomatic, CD4 > 350/ $\mu$ l	Defer treatment		Defer treatment
Asymptomatic, 350/ $\mu$ l < CD4 < 500/ $\mu$ l	Defer treatment	Treat if viral load > 100,000 Consider treatment if 50,000 < viral load < 100,000	Defer treatment
Asymptomatic, CD4 > 500/ $\mu$ l	Defer treatment	Treat if viral load > 100,000 Defer treatment if viral load < 100,000	Defer treatment

\*European AIDS Clinical Society Euroguidelines Group

55,000 copies/mL, US experts acknowledged the fact that « certain experienced clinicians recommend initiating therapy, recognising that the 3-year risk for untreated patients to experience AIDS is > 30% » [32].

It should be noted that initiation of treatment at a CD4 count > 350  $\mu$ L has been shown to significantly reduce the risk (admittedly relatively low in this CD4 count range) of clinical progression [35]. In addition, the CD4 count nadir reached by an individual patient may well have longer term consequences such as the possibility to undertake safe treatment interruption, the success or failure of specific immune-based therapy, or even the development of some complications such as lymphoma. An illustration of the importance of the CD4 count nadir comes from a study showing that, among HAART-treated patients with undetectable viral load and a CD4 count of more than 450  $\mu$ L, the CD4 nadir, not the current CD4 count, was predictive of the response to immunisation with recall antigens [36].

In conclusion, the problem of when to start antiretroviral therapy may certainly still be considered an open question, the answer to which is susceptible to evolve with further studies, even if current guidelines provide a reasonable and pragmatical consensus adapted to the « state of the art ». The fear of long-term complications obviously represents a major element of these recommendations, and cohort studies provided evidence that deferring treatment initiation was not deleterious in the mid term. However, further studies may reinforce the idea that letting patients go to a low CD4 count nadir is deleterious, which may in turn favour an earlier initiation of antiretroviral treatment.

## LIMITATIONS OF HAART

### Failures

In large cohorts, virological success of HAART is obtained in 70-90% of cases, in patients starting their first-line HAART regimen [32]. Adherence to treatment, which is not always easy to obtain, due to patient's difficulties with drugs or to regimen complexity, is a crucial determinant of success [37,38], because a virus that is allowed to replicate in the presence of infra-therapeutic concentrations of drugs will select mutations associated with resistance. Pharmacological interactions with drugs that are inducers of the cytochrome P450-3A4 are also a cause of suboptimal plasma concentrations of protease inhibitors and non-nucleosidic reverse transcriptase inhibitors, of virological rebound and eventually of the selection of resistance mutations. Patients who were exposed to suboptimal regimens before the HAART era have often selected viral strains with mutations making them resistant to nucleoside analogues. More generally, patients with failure of several HAART regimens, because of poor adherence or other causes, pose a difficult therapeutic problem to clinicians, given the pattern of HIV cross-resistance to drugs, and new drugs with different resistance mutations profiles are urgently needed for these patients [39].

### HIV Reservoirs and Proviral DNA Stock

Even in patients with complete virological success (i.e. undetectable plasma HIV RNA load from the first few

months on HAART on), residual replication occurs within cells, and a pool of latently infected cells, that are not sensitive to the effect of antiretroviral drugs support potential reactivation of HIV replication [4]. HAART is only virustatic, i.e. only active on replicating virus, and the stock of proviral DNA within cells virtually stops decreasing after 2 years on therapy [40]. This is reflected by a calculated half-life of 44 months for latently infected cells [41]. In other words, HIV eradication is not reachable with current regimens. Besides, this indicates that there is probably no virological benefit of very long-term treatment beyond the control of active replication : HAART is not able to significantly reduce the stock of proviral DNA below a certain plateau.

It must also be borne in mind that certain anatomical compartments [central nervous system, genital tract] are not easily reached by certain drugs, which allows compartmented replication of HIV in these so-called « sanctuaries », as reflected by the archiving and replication of strains with resistance mutations patterns that are different from those found in plasma and blood cells [42].

### Are there Limitations to Immune Restoration ?

In relation with the limited effects of HAART on HIV reservoirs, CD4 recovery may also level off after a few years on HAART, even in the setting of controlled viremia [40, 43], although there seems to be a potential for long-term regeneration of the peripheral CD4 cell pool [44]. This should be kept in mind along with, as exposed above, the incomplete correction of the T-cell repertoire, the possible occurrence of autoimmune disease in severely immunocompromised patients, the uncertain restoration of HIV-specific immune response, and the possible impact of the CD4 count nadir on the kinetics and the degree of immune restoration, as indicators of the fact that immune reconstitution on HAART, although sufficient to prevent and control opportunistic agents, should probably not be understood as a return to normal. Again, all of these arguments would plead for an earlier treatment initiation than currently recommended.

## SIDE EFFECTS OF HAART

### Short-term Side Effects

Antiretroviral drugs may have short-term side effects, such as digestive intolerance (protease inhibitors, zidovudine), central nervous system disorders (efavirenz) hepatotoxicity (protease inhibitors, zidovudine, didanosine) or hypersensitivity reactions (abacavir, nevirapine) [45]. These unwanted effects must be clearly explained to patients because they may have a strong impact on adherence, and some of them, such as hypersensitivity reactions, may necessitate immediate reaction and definitive drug withdrawal.

### Mitochondrial Toxicity

Nucleosidic inhibitors of the reverse transcriptase (NRTI) share, at varying degrees, potential toxicity on mitochondria, *via* interference with DNA polymerase [47]. Mitochondrial toxicity is the cause of most, if not all, mid- and long-term

side effects of NRTIs, such as peripheral neuropathy (didanosine, zalcitabine, stavudine), myopathy or myocardiopathy (zidovudine), hepatitis (zidovudine), pancreatitis (didanosine, zalcitabine, stavudine), and it most certainly contributes to the lipoatrophic component of the lipodystrophy syndrome observed in HAART-treated patients [48-51].

Although the incidence is difficult to measure, many patients complain of a syndrome of mitochondrial dysfunction, with fatigue, muscle and abdominal pain, inconstantly associated with hyperlactatemia, which is not a very sensitive index of mitochondrial dysfunction. The incidence of symptomatic hyperlactatemia has been estimated at 0.5-1/100 patient-years in cohorts of patients treated with nucleoside analogues [52,53]. Some patients (roughly 1/1000) will present with lactic acidosis, a life-threatening condition requiring intensive care and drug cessation [54].

### **Metabolic Disturbances, Effects on Cell Differentiation and Cardiovascular Risk**

One major concern in patients on HAART is the occurrence of the lipodystrophy syndrome (peripheral lipoatrophy and central, visceral lipohypertrophy). In addition to the esthetic and psychological prejudices caused by morphological changes, this syndrome is often accompanied by disturbances of the glucid and lipid metabolism, with hyperinsulinemia, glucose intolerance or overt diabetes, hypertriglyceridemia and hypercholesterolemia (high LDL and low HDL), that also appear independently of clinical abnormalities of fat distribution [55-57]. This rose the question of an increased cardiovascular risk in patients treated with HAART for a long time, the more so since HIV cohorts are ageing, which is a positive consequence of HAART efficacy, they are more exposed to cigarette smoking than the general population, and may have personal, unmodifiable cardiovascular risk factors, such as a family history of myocardial infarction and stroke. As a matter of fact, large cohort studies indicate that the risk of myocardial infarction augments with time on HAART (26% per year), in HIV-infected patients, and that the measured risk in the male population on a protease inhibitor-including HAART regimen represents a 3-fold increase as compared to the general population of same gender and age [58,59] (Table 2). Globally, these results clearly indicate that time on HAART represents an independent risk factor for myocardial infarction, that is added to classical risk factors, such as age, male sex, smoking, previous cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, and diabetes. It should also be noted that these studies underline the responsibility of protease inhibitor-containing regimens in the cardiovascular risk, because these are the regimens that have been taken with the longest duration at the present time : whether regimens based on non-nucleoside reverse transcriptase inhibitors convey the same risk remains to be determined.

However, these important results should have a strong impact on the implementation of cardiovascular risk prevention in HAART-treated patients (counselling on

smoking cessation and exercise, treatment of glucid and lipid disorders).

Lipodystrophy, related metabolic abnormalities and atherogenesis in HAART-receiving patients probably represent a complex, multifactorial syndrome, but the mitochondrial toxicity of NRTIs and the effects of protease inhibitors on cell differentiation are most certainly involved in their pathogenesis.

Several protease inhibitors have been shown to interfere, at different degrees, with murine preadipocyte differentiation *in vivo* : cells appear morphologically abnormal, with low triglyceride contents, are more sensitive to apoptosis (an effect favoured by the addition of nucleoside analogues), with a low expression of transcription factors linked to their differentiation into mature adipocytes (e.g. SREBP-1) [60,61], possibly linked to an abnormal maturation of nuclear lamin A/C [62]. These abnormalities have also been found *in vivo*, in the atrophic subcutaneous adipose tissue of lipodystrophic patients, where an excessive expression of TNF has also been described [63].

In a mouse model, protease inhibitors have also been shown to favour the *in vitro* transformation of macrophages into foam cells, via the overexpression of CD36, and to induce atherosclerosis, independently of the induction of hyperlipidemia [64]. These experimental data are in keeping with preliminary clinical observations suggesting that patients on HAART with a protease inhibitor are exposed to an accelerated atherogenic process. These patients have a greater carotid intima-media thickness than controls, apparently with faster progression with time, and present with indices of endothelial dysfunction, such as higher blood pressure and abnormal flow dilatation responses [65,66].

In conclusion, patients on HAART regimens, especially on protease inhibitor-including combinations, for years appear to be at an increased risk for cardiovascular events, linked to the time on drugs, and the possibility exists that these complications become a major concern for patients and physicians in the long-term, although they obviously do not outweigh the benefits of HAART at the present time.

### **SYNTHESIS : THE DILEMMA OF STARTING AND MAINTAINING ANTIRETROVIRAL THERAPY**

The data summarized above point to two major difficulties : When should a treatment be started ? and : How long should a treatment be prolonged ? Treatment is necessary in order to maintain viral replication as low as possible, and to allow immune function recovery or preservation. It is well known that treatment interruptions almost invariably result in viral rebound [67], with possible consequences on the CD4 count. However, long exposure to drugs may result in severe toxicity and apparently increases the risk of cardiovascular events. In addition, very long-term maintenance of treatment does not result in a significant reduction of the HIV DNA stock after 2 years, and will not allow viral eradication. Current recommendations tend to delay treatment initiation, although this may lead to suboptimal immune restoration, particularly to HIV-specific antigens, which could hinder the efficacy of immune-based therapy or the safety of treatment interruption. This could be

**Table 2. Main Results of Two Major Studies on the Incidence of Myocardial Infarction in HAART-treated Patients**

	Study	
	D:A:D study [58]	Mary-Krause <i>et al.</i> [59]
Type of study	Prospective	French hospital database
Number of patients	23,468	34,976
PY of follow up	36,199	88,029
Sex ratio of population	75.9% males	100% males
Age (years)	39 (34-45)	Patients without MI: 37.7 ± 9.1 Patients with MI: 41.9 ± 8.2
Median exposure to antiretrovirals [years(IQR)]	On antiretrovirals : 2.8 (0.6-4.5)	On antiretrovirals :
		Patients without MI: 2.8 (1.2-4.5) Patients with MI: 2.9 (1.7-4.8)
		On PI :
		Patients without MI: 2.1 (1.2-2.9) Patients with MI: 1.7 (1.1-2.6)
HAART regimens	PI (67.1%) and NNRTI-including	PI- and NNRTI-including, focussed on PI
Number of MI	126	60 (49 on PI)
Relative risk of MI (95% confidence interval) with time on HAART	<1yr on HAART : 1 No exposure to HAART : 0.24 (0.07-0.89) 1 yr exposure < 2 yrs : 1.34 (0.58-3.10) 2 yr s exposure < 3 yrs : 1.73 (0.80-3.76) 3 yrs exposure < 4 yrs : 1.98 (0.94-4.15) exposure > 4 yrs : 2.55 (1.25-5.20)	<18 months on PI : 1 18-29 months on PI : 1.9 (1.0-3.1) 30 months on PI : 3.6 (1.8-6.2)
Standardised morbidity ratio as compared to general population of same age and sex	Not available	<18 months on PI : 0.8 (0.5-1.3) 18-29 months on PI : 1.5 (0.8-2.5) 30 months on PI : 2.9 (1.5-5.0)
Other risk factors associated with MI*	Age, male sex, smoking, previous cardiovascular disease, hypercholesterolemia, hypertriglyceridemia, diabetes	Age

PY : patient-years ; IQR : interquartile range ; MI : myocardial infarction ; PI : protease inhibitors, NNRTI : non-nucleoside reverse transcriptase inhibitors

\* According to study design, some risk factors could not be examined in [59].

an argument for earlier treatment initiation, i.e. longer exposure to drugs and greater risk of side effects.

The resulting dilemma is that the desirable very long-term maintenance of antiretroviral treatment might ultimately result in side effects that will outweigh its virologic and immunological benefit.

### WHAT FUTURE STRATEGIES?

#### Better Criteria for Treatment Initiation?

One possibility is that current criteria for treatment initiation may not be as accurate as one would expect. Recent data indicate that, in addition to HIV RNA and CD4 count, the level of HIV-1 DNA in peripheral mononuclear cells has an independent prognostic value for the occurrence of death, of AIDS-defining events and of the CD4 count going below 200/ $\mu$ L [68,69]. Even among patients with a treatment indication based on the CD4 count and plasma RNA level, some have low HIV DNA levels predicting a slow evolution: these patients could possibly « escape »

treatment for a few more years, and thus experience a lesser risk of appearance of mid and long-term complications of HAART [68].

#### Structured Treatment Interruption?

Structured treatment interruptions (STI) have been proposed as a means to solve the contradiction between maintenance of treatment and inherent side effects. To date, little information supports the idea that STI may prevent long-term complications of HAART. Besides, contrary to expectations (a possible « auto-vaccination » effect) there seems to be no immunological benefit in STI, and in some studies, patients have experienced virological failure and the appearance of resistance mutations [70-72].

However, STI may still represent a valid drug-sparing strategy, providing that criteria be validated for selecting patients with a high probability of benefiting from long interruptions before reaching the criteria for treatment resumption: the proviral DNA level [68] or the CD4 count nadir [73], or both, could be these ultimate criteria.

### Immune-based Treatment Strategies ?

Immune-based treatment strategies may be instrumental in helping to solve the problem of life-long antiretroviral treatment. Non specific immune-based strategies rely on the use of cytokines, currently Interleukin 2 (IL-2) and interferon alpha (IFN ).

It has been demonstrated in several trials that IL-2 allows a CD4 count restoration superior to that obtained with antiretroviral treatment alone (dual NRTI therapy or HAART) in patients with conserved CD4 counts [74,75] and in patients with less than 200 CD4 cells/ $\mu$ L in spite of a good virological control [76]. IL-2 induces peripheral cell proliferation, prolongation of T-cell life duration, and possibly enhanced thymopoiesis. Whether this translates in clinical benefit to patients is currently being tested in large prospective trials. Another possibility which is actively explored in ongoing trials is that, IL-2 could be helpful in preparing HAART interruption or in delaying HAART initiation in treatment-naïve patients.

IFN has been shown to help in reducing the proviral DNA stock in patients receiving HAART at the time of HIV primary infection [77]. Trials are ongoing in HAART-treated patients to test whether IFN could also be useful in preparing HAART interruption.

The underlying concepts of these trials of IL-2 and IFN is that, through their effects on the CD4 population or antigen-presenting cells, they could disconnect immune recovery from viral replication control, and/or reinforce the ability of immune effectors to control replication. IL-2 has also been shown to improve immune restoration, as compared to HAART alone, since cellular responses to recall antigens are better in IL-2 treated patients [75]. Thus, non-specific immune-based therapy could hopefully reduce the need for antiretrovirals, by either allowing to delay their initiation or to prolong off-treatment periods.

Specific immunotherapy (therapeutic vaccination) could also be developed with the same goals: very preliminary results suggest the validity of this concept [78-79], although much work is still needed on the vaccine preparation, the administration strategy, and the definition of target patients.

### HOW CAN BETTER DRUGS BE DESIGNED ?

As exposed above, reasonable hope lies in the better utilisation of existing drugs, due to the development of innovative strategies. However, there is obviously a need for better drugs, and one can speculate on what could be done to enhance virologic efficacy on the one hand and tolerance on the other hand.

Obviously, no treatment allowing viral eradication will be made available within a foreseeable time scale. However, drugs with higher intrinsic antiviral efficacy can be developed against « classical » targets (reverse transcriptase and protease) or new targets (fusion between virus and cell membrane, entry into cells, integration of viral DNA). Enhancing affinity and specificity for viral targets (as opposed to related cellular enzymes), possibly through computerised modelling of drugs (as done for protease inhibitors), is a way of improving drug efficacy. Elaboration

of new compounds from existing drugs to enhance affinity for target, intra-cellular half-life, and to overcome viral resistance, is another axis of progress. New combinations of new drugs could hopefully prove more powerful and less toxic than current regimens.

Tolerance has now become a major concern, especially the adipocyte/metabolic toxicity issue. New drugs in development should definitely be tested for toxicity on (pre-) adipocyte cell lines: what are their effects on cell differentiation and lipid content ? on the expression of adipocyte key transcription factors and nuclear lamin maturation ? on adipose cell viability and apoptosis ? More generally, what is the effects of drugs on mitochondrial DNA content and functions in a variety of cell types ? An important aspect would be the systematic testing of new drugs, both individually and in association with other common antiretrovirals, reflecting the usual situation of combination therapy. Standardised conditions of drug testing on cell lines should be developed and used for assessing drug toxicity.

Animal models (e.g. rat) of *in vivo* toxicity should be used to assess the effects of drugs on glucid/lipid metabolism on standard and lipid-rich diets, and on body composition (adipose tissue measurement and repartition) in the short and mid terms. Studies in healthy volunteers should also be specifically designed to address these issues (It should be remembered that studies demonstrating the induction of hyperlipidaemia and insulin resistance in healthy volunteers by PIs were performed years after drug approval), and, as has now become standard, phase I and II studies must include metabolic / adipose tissue measurements.

### CONCLUSION: WHAT SHOULD BE DONE WITH HAART FAILURES ...AND SUCCESSES ?

In conclusion, HIV therapy is currently entering a new era. HAART has shown its efficacy in most patients but two major difficulties are arising. First, patients experiencing treatment failure are at a crucial need for new therapeutic options. Second, patients experiencing virological success on their current HAART regimen may be exposed to severe complications in the long-term. In the latter case, new strategies, or less probably totally innocuous new drugs, are urgently needed.

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