

HIV/AIDS

Antiretroviral Newsletter



WORLD HEALTH ORGANIZATION

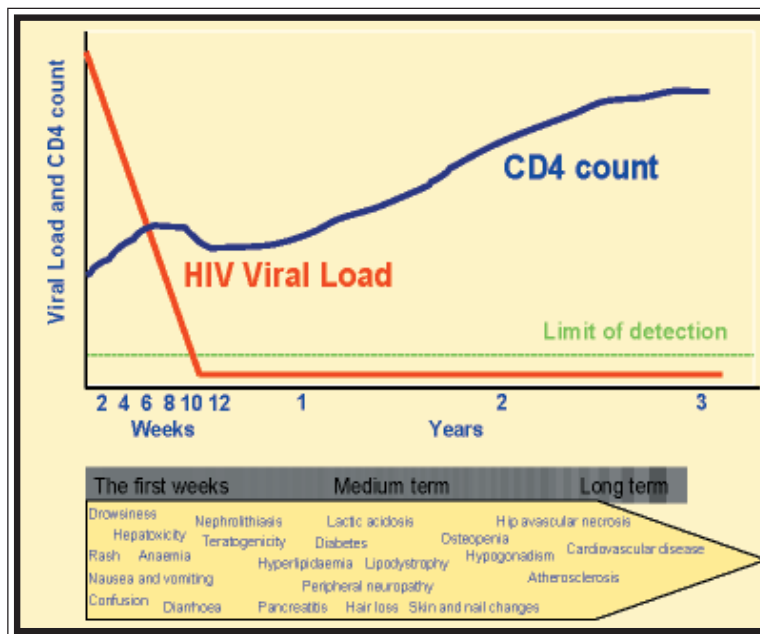
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The aim of this biannual newsletter is to provide health workers in the Region with a brief, up-to-date summary of the latest developments in antiretroviral therapies.

MANAGING ANTIRETROVIRAL SIDE EFFECTS A PRACTICAL GUIDE

Figure 1: Goals of therapy and common ARV side effects



INTRODUCTION

This newsletter reviews the side effects of antiretroviral therapy according to the timeframe after initiating therapy at which these side effects are expected to occur. In general, antiretroviral toxicities can be divided into three time-related groups:

- Early side effects (within the first days to weeks)
- Medium-term side effects (occurring within the first months of therapy)
- Late side effects (typically in the second and subsequent years)

There is considerable overlap within these groupings and many side effects can occur at any time during therapy. Recognition of therapy-related adverse events and decisions to intervene require knowledge of both class-

specific and individual drug toxicities. Drug interactions also complicate antiretroviral therapy, increasing toxicity or the risk of treatment failure. Tables that list drugs which adversely interact with antiretrovirals are available^{1,2} and interactive websites allow physicians to enter drug combinations and receive accurate information on possible interactions.³

SWITCHING THERAPY

There are two main reasons to switch therapy: toxicity and treatment failure. Economic and drug supply factors may also result in the need to switch. The general principle is that all drugs in the regimen are switched in the case of treatment failure and that individual drug substitutions can be made in the case of toxicity and intolerance

SIDE EFFECTS IN THE FIRST DAYS AND WEEKS OF THERAPY

RASH

Rashes are most common with non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), especially nevirapine. The rate is 10% to 20%.^{4,5} Most rashes occur within the first 12 weeks and often within the first week. Patients need to be warned of the possibility of rashes and clear communication links need to be set up between the treatment team and the patient. In the case of maculopapular rashes that are mild without systemic symptoms (fever, abnormal liver enzymes, arthralgia) a “treat through” approach may allow the patient to continue on the therapy. Antihistamines, such as loratadine 10 mg BID, will help to relieve symptoms. Careful observation is required during the treat through period with daily visits or (if not possible) telephone contact until it is clear if the rash will resolve or worsen. It should be apparent within 2-3 days if an NNRTI-induced rash will be self-limiting, as is mostly the case with efavirenz. It is more likely that a nevirapine-induced rash will require cessation of that drug.⁶ Severe reactions occur in about 1% of patients and include Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN) and drug rash eosinophilia and systemic symptoms (DRESS), with fever and multiple organ involvement. Other antiretrovirals associated with rashes are amprenavir, indinavir, zidovudine and stavudine.

MANAGEMENT

Rashes associated with systemic symptoms and rashes characterized by desquamation and skin or mucosal blistering will normally require permanent cessation of the drug. A common approach is to stop all drugs in the combination, wait until the symptoms resolve and restart a new combination without the offending drug. Patients with a nevirapine-induced rash may be able to tolerate efavirenz.⁷ Abacavir may cause a rash as part of a hypersensitivity reaction in approximately 5% of patients who take it. Patients with an abacavir hypersensitivity reaction should never be re-challenged with the drug as this can precipitate a life threatening reaction.

CENTRAL NERVOUS SYSTEM (CNS) EFFECTS

Drowsiness (and insomnia), dizziness, confusion, and vivid dreams are associated with the use of efavirenz (5.5% in the 2NN study). These symptoms are normally self-resolving but can take weeks to months to completely resolve.

MANAGEMENT

Alert patients of the possibility of these side effects, advise them to take efavirenz just before going to sleep and to persist with the drug as the symptoms will usually improve within weeks. Replace efavirenz with nevirapine if the symptoms persist and are unacceptable to the patient.

HEPATOTOXICITY

Elevation of liver enzymes (ALT, AST) and symptoms of hepatitis (jaundice, anorexia, dark urine) may be associated with all antiretrovirals and occur more frequently in those co-infected with hepatitis B virus or hepatitis C virus. Hepatotoxicity in the first weeks of therapy is most commonly associated with nevirapine. It is also associated with nucleosides, especially AZT, d4T and ddI and protease inhibitors, most commonly with ritonavir.

MANAGEMENT

Monitor liver enzymes at baseline, after one month and then every three months if laboratory resources are available. If not, monitor for clinical symptoms of hepatotoxicity. Stop the implicated drug and replace it if patient has clinical hepatitis or elevation of liver enzymes greater than five times the upper limit of normal.

TERATOGENICITY

Efavirenz and the combination of ddI + d4T are contraindicated in pregnancy. These drugs should be avoided in women who are pregnant or considering pregnancy.

ANAEMIA

Anaemia is mostly associated with zidovudine use. Sudden and acute zidovudine bone marrow suppression can occur within the first weeks of therapy or present as a slow onset of progressive anaemia over months.

MANAGEMENT

Monitor haemoglobin or hematocrit before and during AZT therapy (monthly for three months then every three months). If significant anaemia occurs (haemoglobin < 9 mg/dL) switch to an alternative nucleoside. Blood transfusion may be needed. Recombinant human erythropoietin (if available) is useful. Vitamin B12 and iron supplements do not help.

GASTROINTESTINAL TOXICITY

Nausea and vomiting can occur in patients taking any of the nucleosides, especially AZT and ddI, and in those taking the protease inhibitors ritonavir, amprenavir and to a lesser extent indinavir. Efavirenz is the most likely of the non-nucleosides to cause these symptoms. Nelfinavir commonly causes diarrhoea.

MANAGEMENT

Taking drugs with food may reduce nausea. However, ddI and indinavir need to be taken without food. Nausea from efavirenz normally is self limiting. Antiemetics such as metoclopramide 10 mg BID and anti-diarrhoeals such as loperamide 10 mg BID are useful to control symptoms. Patients taking nelfinavir may need to take loperamide continuously to control diarrhoea.

MEDIUM-TERM SIDE EFFECTS

LACTIC ACIDOSIS

d4T, ddI (and, to a lesser extent, other nucleosides such as AZT, 3TC and abacavir) have been associated with life-threatening lactic acidosis. The mechanism is via the mitochondrial toxicity induced by these drugs.⁸ The patient typically presents symptoms after six months or more on antiretroviral therapy with unexpected clinical deterioration characterized by weakness, weight loss, abdominal pain and distension, anorexia, nausea, vomiting and diarrhoea. Abnormal blood chemistry includes elevated serum lactate and elevated ALT, LDH and CPK and abnormal anion gap, sodium-[chloride+CO₂].

MANAGEMENT

Alert patients to report any unexpected deterioration in their general health, especially when their viral load and CD4 count (if available) are responding to therapy. Stop all antiretrovirals. Recovery is slow with an average of 60 days for normalization of serum lactate levels. Thiamine or riboflavin (at least 30 mg/day) may be effective. If the patient is unwell, hospitalization may be required for mechanical ventilation, dialysis, intravenous bicarbonate, and other life-support measures. Many deaths have been reported. Restart antiretrovirals after full recovery using a combination of non-nucleosides and protease inhibitors.

PERIPHERAL NEUROPATHY

Peripheral neuropathy is associated with the use of the dideoxynucleosides (“D” drugs) d4T, ddI and ddC and especially with the combination of ddI and d4T.⁹ Incidence varies by drug, dose and duration of nucleoside therapy and stage of HIV disease with 12% to 66% reported in “D” drug studies and <5% in patients with well-preserved CD4 counts.¹⁰ Peripheral neuropathy presents with numbness, hyperaesthesia or dysaesthesia and episodic shooting pain, usually beginning in the lower extremities. Ankle reflex is usually reduced or absent and there is reduced pinprick, temperature, vibratory and proprioceptive sensation.

MANAGEMENT

Stop the drug if possible. There may be a “coasting” period, typically about 4 to 8 weeks, during which symptoms intensify after drug withdrawal. Analgesics are usually ineffective and drugs used to treat neuropathic pain (amitriptyline 25-500 mg before bed, sodium valproate 200-1500mg/day, flecainide 50-100 mg 2-3 times daily) maybe of some use.

PANCREATITIS

The most common causes of acute pancreatitis are ddI and d4T. The relative risk of pancreatitis is twice as great with the combination of d4T and ddI as with ddI alone.¹¹ Among antiretroviral agents, ddI is most frequently cited in case reports.

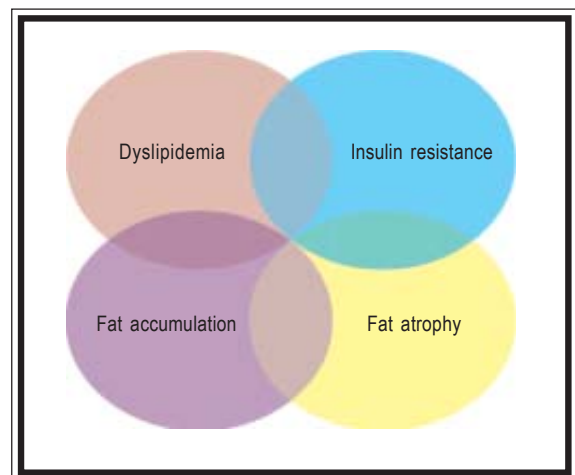
The incidence of pancreatitis is 1% to 7% in patients taking ddI and is fatal in about 10% of cases. High triglyceride levels (>5-10 times the upper limit of normal) caused by protease inhibitors also carry an increased risk of pancreatitis. Clinical presentation is central upper abdominal pain with or without nausea and vomiting. Serum amylase and lipase levels should be measured as part of the initial evaluation of acute pancreatitis, but absolute values are not prognostic. The amylase level can be normal in up to 30% of patients with acute pancreatitis.¹²

MANAGEMENT

Stop all drugs until resolved and replace offending drug in the new regime. Supportive care (often requiring hospitalization) is with analgesics and intravenous fluids.

LONG-TERM SIDE EFFECTS

Figure 2: Overlapping metabolic toxicities caused by antiretrovirals



DYSLIPIDEMIA

Protease inhibitors, in particular, cause dyslipidemia (elevation of serum cholesterol and triglyceride levels). In comparative studies, dyslipidemia has been observed with increasing frequency and severity from atazanavir (lowest) to saquinavir to nelfinavir to lopinavir/ritonavir (highest).^{13,14} However, nucleosides such as d4T and non-nucleosides, such as efavirenz can also cause this problem. While dyslipidemia can occur at any time, elevated lipids requiring intervention are typically seen after six months or more on antiretroviral therapy.

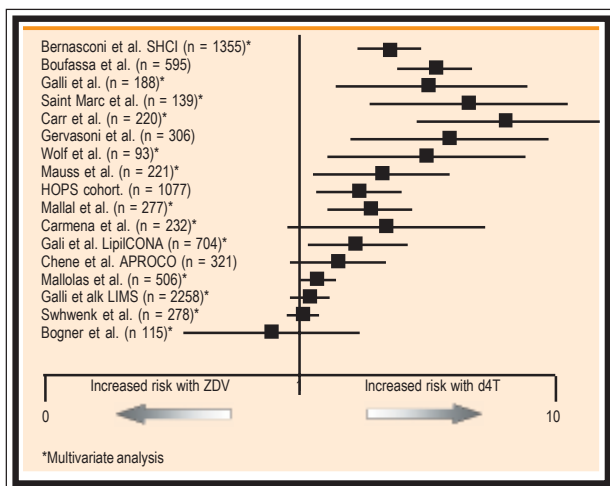
MANAGEMENT

The first-line approach is to reduce dietary fat intake, to increase exercise and to avoid smoking. Switching to a triple nucleoside regimen such as Trizivir or to a non-nucleoside based regimen is rational. If lipid lowering medication is required, the International AIDS Society USA guidelines for management of metabolic complications of HIV therapy recommend use of gemfibrozil or fenofibrate for hypertriglyceridaemia, or pravastatin or atorvastatin for elevated cholesterol.¹⁵ The main concerns have been efficacy and drug interactions, primarily with protease inhibitors. This accounts for the preferential use of atorvastatin and pravastatin with avoidance of lovastatin and simvastatin. The goals of therapy are to reduce fasting triglyceride levels to <750-1 000 mg/dL and LDL cholesterol <160 mg/dL. Doses of the drugs are the same as for other patients requiring lipid lowering therapy.

LIPODYSTROPHY

The body composition changes associated with this syndrome are peripheral fat loss in arms, buttocks and legs; facial fat wasting; central fat accumulation (buffalo hump, increased abdominal fat, breast enlargement and lipomas); and ingrown toenails. These changes are seen in patients who take protease inhibitors and those taking nucleosides, especially d4T and ddI. Up to 80% of patients report changes in their body shape typically after 9-12 months of therapy

Figure 3: Relative risk of lipodystrophy with zidovudine compared with stavudine¹⁶



MANAGEMENT

Fat loss is likely to be permanent in most cases. Alert the patient and intervene early with revision of the drug regimen if possible (e.g. switch d4T to AZT). Switching may stop further fat loss. Clinical trials have studied the use of the oral hypoglycaemic agents (glitazones and fibrates), growth hormone, anabolic steroids and testosterone replacement therapy in men. No treatment so far has shown consistent benefit. Cosmetic surgery is

the most successful treatment with injections of polylactic acid or collagen resulting in improvement in facial features.

CARDIOVASCULAR DISEASE

The Data Collection on Adverse Events of Anti-HIV Drugs study (23 468 participants with a median age of 39 years) demonstrated that, for every year an individual was exposed to combination antiretroviral therapy, the risk of myocardial infarction was increased by 26%.¹⁷

MANAGEMENT

The implication of this and other data is that there is a need for more aggressive management of risk factors for future cardiovascular disease such as high cholesterol and a need to choose drugs within classes and across classes to limit the long-term lipid and insulin side effects of therapy.

HYPERGLYCAEMIA AND INSULIN RESISTANCE

All protease inhibitors (PI) interfere with insulin-induced glucose metabolism.¹⁸ The result is hyperglycaemia and diabetes, reported in 3%-17% of protease inhibitor recipients. While symptoms can occur as early as two months after commencing PI therapy, the average is about 5% at five years.¹⁹

MANAGEMENT

Alert the patient to the problem and the symptoms to watch for (i.e. polyuria, polydipsia and weight loss). Monitor fasting blood sugar levels every three months in patients taking PIs. Stop the PI if this is an option. This strategy may not resolve the diabetes which can be permanent. If treatment is needed, use oral hypoglycaemic agents (metformin or glitazones). Insulin may be required. Dieting is probably not helpful.

DO THE NEW DRUGS OFFER A SAFER FUTURE?

ATAZANAVIR (REYATAZ)

This new protease inhibitor, designed for once-daily dosing, was approved by the Food and Drug Administration (FDA) in early 2003. Studies show that it is at least equal in potency to nelfinavir when used in similar combinations.²⁰ Studies have shown that atazanavir has less impact on cholesterol and triglyceride levels compared to other protease inhibitors, probably resulting in reduced risks of fat redistribution and cholesterol-related problems (including fatty liver) that have been seen with the other protease inhibitors.²⁰ Patients switching from nelfinavir to atazanavir had reductions in total cholesterol and triglyceride levels by 16% and 28% respectively 12 weeks after the switch. In another study, BMS 034, there were no increases in total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides in patient taking atazanavir for 48 weeks in combination with AZT and 3TC.

EMTRICITABINE (FTC, COVIRACIL)

FTC, like 3TC, has few side effects and these occur rarely.²¹ The most common ones are headache, diarrhoea, nausea and rash. It is taken as one 300 mg tablet per day and exhibits the same resistance pattern as 3TC (high level resistance with a single point mutation).

ENFUVRTIDE (T20, FUZION)

The first and only FDA licensed fusion inhibitor, enfuvirtide, has shown durable virological response in 48-week data.²² Delivered as a twice-daily subcutaneous injection of 90 mg, the main side effect was mild to

moderate injection site reactions, with no patients stopping treatment due to side effects. Treatment-related diarrhoea and nausea were also reported.

TENOFOVIR (VIREAD)

The side effects of tenofovir are nausea, diarrhoea, vomiting and flatulence. In animal studies using much higher dosages, a loss of bone density developed. Renal impairment, including cases of acute renal failure and Fanconi syndrome (renal tubular necrosis with hypophosphataemia), has been reported (rarely) in association with the use of tenofovir.

**Table 1: Laboratory Side Effects Of Antiretroviral Therapy
(Source: Project Information Website)**

PROTEASE INHIBITOR							
	APV	IDV	LPV	NFV	RTV	SQV ¹	SQV ²
Anaemia							
Leucopaenia							
Neutropaenia							
Thrmboctopenia							
Elevated Alkaline Phosphatase							
Elevated Amylase (pancreatitis)							
Hyperbilirubinaemia							
Hypercholesterolemia							
Elevated Creatinine							
Hyperglycaemia							
Elevated Liver Function Tests (AST, ALT)							
Hypertriglyceridaemia							

APV=Amprenavir; IDV=Indinavir; LPV=Lopinavir; NFV=Nelfinavir; RTV=Ritonavir; SQV=Saquinavir
1. hard gel capsule 2. soft gel capsule

NON-NUCLEOSIDE REVERSE TRANCRIPASE INHIBITORS			
	DLV	EFV	NVP
Anaemia			
Leucopaenia			
Neutropaenia			
Thrmboctopenia			
Elevated Alkaline Phosphatase			
Elevated Amylase (pancreatitis)			
Hyperbilirubinaemia			
Hypercholesterolemia			
Elevated Creatinine			
Hyperglycaemia			
Elevated Liver Function Tests (AST, ALT)			
Hypertriglyceridaemia			

DLV=Delavirdine EFV=Efavirenz NVP=Nevirapine

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS								
	ABC	AZT	Combivir	Trizivir	ddC	ddl	d4T	3TC
Leucopaenia								
Neutropaenia								
Thrmocytopenia								
Elevated Alkaline								
Elevated Amylase								
Hyperbilirubinemia								
Hypercholesterolemia								
Elevated Creatinine								
Hyperglycaemia								
Elevated Liver								
Hypertriglyceridaemia								

ABC=Abacavir, AZT=Zidovudine; >15% of people in clinical trials
 Combivir=AZT+3TC; 5%-15% of people in clinical trials
 Trizivir=AZT+3TC+ABC <5% of people in clinical trials

ACKNOWLEDGEMENTS

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REFERENCES

¹ *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents.* Department of Health and Human Services (DHHS), July 14 2003.

Available at <http://www.hivatis.org>.

² *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Guidelines for a Public Health Approach.* April 2002, World Health Organization, April 2002, (ISBN 9241545674) and <http://www.who.int>.

³ <http://hivinsite.ucsf.edu/InSite.jsp?page=ARV>

⁴ Bossi P, Colin D, Bricaire F, Caumes E. Hypersensitivity syndrome associated with efavirenz therapy. *Clin Infect Dis* 2000, 30:227-8.

⁵ Fagot JP et al. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *AIDS* 2001, 15:1843-8.

⁶ van Leth F et al. *Lipid changes in a randomized comparative trial of first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine (2NN Study).* 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, Massachusetts. Abstract 752.

⁷ Clarke S, Harrington P, Barry M, Mulcahy F. The tolerability of efavirenz after nevirapine-related adverse events. *Clin Infect Dis*, 2000, 31:806-7.

⁸ Cote HC et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *N Engl J Med*, 2002, 346:811-820.

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- ⁹ Wulff EA, Wang AK, Simpson DM. HIV-associated peripheral neuropathy: epidemiology, pathophysiology and treatment. *Drugs*, 2000, 59:1251-1260.
- ¹⁰ Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol*, 1995, 9:153-161.
- ¹¹ Moore RD, Keruly JC, Chaisson RE. Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS*. 2001, 15:617-620.
- ¹² Aboulafia DM. Acute pancreatitis: a fatal complication of AIDS therapy. *J Clin Gastroenterol*. 1997;25: 640-645.
- ¹³ Murphy R et al. *Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or ATV: 108-week results of BMS study 008/044*. Program and abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, Massachusetts. Abstract 555.
- ¹⁴ Walmsley S et al. M98-863 Study Team. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med*. 2002, 346:2039-2046.
- ¹⁵ Schambelan M et al. International AIDS Society-USA. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS Society-USA panel. *J Acquir Immune Defic Syndr*; 2002, 31:257-275.
- ¹⁶ White AJ. Mitochondrial toxicity and HIV therapy. *Sex Transm Infect*, 2001, 77:158-173.
- ¹⁷ Friis-Møller N et al. *Exposure to HAART is associated with an increased risk of myocardial infarction: The DAD Study*. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, Massachusetts. Abstract 130.
- ¹⁸ Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999;353:2093-9.
- ¹⁹ Mulligan K et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. *J Acquir Immune Defic Syndr* 2000;23:35-43.
- ²⁰ Murphy R et al. *Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or ATV: 108-week results of BMS study 008/044*. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, Massachusetts. Abstract 555.
- ²¹ Molina JM et al. *Once-daily combination of emtricitabine, didanosine, and efavirenz vs continued PI-based HAART in HIV-infected adults with undetectable plasma HIV-RNA: 48-week results of a prospective randomized multicenter trial (ALIZE-ANRS 99)*. 10th Conference on Retroviruses and Opportunistic Infections, February 10-14, 2003, Boston, Massachusetts. Abstract 551.
- ²² Lalezari J.P et al. A Phase II Clinical Study of the Long-Term Safety and Antiviral Activity of Enfuvirtide-Based Antiretroviral Therapy: *AIDS*, 2003, 17(5):691-698.



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