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Fact Sheets on Antiretroviral Drugs

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ABBREVIATIONS AND ACRONYMS USED IN THE TEXT

3TC	Lamivudine
ABC	Abacavir
ALT	Alanine Transaminase
APV	Amprenavir
ART	Antiretroviral Treatment
AZT/ZDV	Azidothymidine, Zidovudine
BHIVA	British HIV Association
CD4	T-CD4+ Lymphocyte
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CT	Computed Tomography
CYP	Cytochrome P450
D4T	Stavudine
DDC	Zalcitabine
DDI	Didanosine
DHHS	Department of Health and Human Services of USA
DLV	Delavirdine
DNA	Deoxyribonucleic Acid
EC	Enteric Coated
EFV	Efavirenz
FDA	Food and Drug Administration
GI	Gastro-Intestinal
HAART	Highly Active Anti-Retroviral Treatment
HGC	Hard Gelatin Capsules
HIV	Human Immunodeficiency Virus
IDV	Indinavir
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoprotein
LPV	Lopinavir

LPV/r	Lopinavir/Ritonavir
NFV	Nelfinavir
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
PI	Protease Inhibitor
r	Ritonavir (when given in association with other PIs for boosting effect)
RNA	Ribonucleic Acid
RTV	Ritonavir
SGC	Soft Gelatin Capsules
SQV	Saquinavir
TB	Tuberculosis
TFV	Tenofovir
UK	United Kingdom
US	United States
WHO	World Health Organization
ZDV/AZT	Zidovudine, Azidothymidine
§	Dose modification of the drug accompanying this symbol is needed/suggested

CONTENTS

INTRODUCTION

The World Health Organization assists countries in the planning and implementation of comprehensive HIV prevention and care.

The continuum of care component includes a referral network extending from home and community care settings, through peripheral health units, to district hospitals. Comprehensive care comprises a proper balance between clinical management, counselling, nursing care and social support. It requires well-informed health care staff, with good communication skills, adequate skills in the recognition, diagnosis and management of HIV-related conditions, working closely with families.

These Fact Sheets form part of a set of materials available to physicians dealing with HIV-infected patients, who have the opportunity to prescribe antiretroviral drugs.

Target Audience

These Fact Sheets and accompanying notes are designed to be employed in the daily activities of physicians responsible for the management of HIV-infected patients at any level.

Features

The set consists of Fact Sheets of all currently approved antiretroviral drugs. The Fact Sheet for each drug includes information about the class of the drug, available formulations, storage, dosage, known interactions with other drugs (including other antiretrovirals) and main side effects.

All the provided information comes from labelling information, data published in WHO documents, international scientific literature, books, reports presented at

international conferences, national guidelines for antiretroviral treatment of different countries and from websites dedicated to the treatment of HIV infection.

Effective use of the Fact Sheets

These Fact Sheets have been prepared as a supplementary source of information for physicians and do not replace the existing current National Guidelines for Antiretroviral Treatment of any country. The information listed here is updated till April 2002. It is proposed to update these fact sheets from time to time.

Antiretroviral treatment is an area where the updating process is continuous; therefore, it is suggested that readers keep themselves informed on the latest news through medical literature and by browsing the Internet at the websites suggested or any other website that can be useful.

The process of choosing the antiretroviral regimen is sometimes a complicated one and many aspects should be considered; however, it is not intended to give any guideline on treatment, but it is suggested that national guidelines be referred. If for any reason – guidelines have not yet been developed in any country, guidelines developed by WHO Regional Office for South-East Asia (New Delhi, India), or WHO – Headquarters, Geneva, the neighbouring countries, the US (DHHS) or UK (BHIVA) may please be referred to.

With the exception of prevention of mother-to-child-transmission of HIV, any kind of antiretroviral mono- or dual therapy should be avoided due to documented emergence of viral resistance.

APPROVED ANTIRETROVIRAL DRUGS

Generic name	Class	Main brand®	Company[1]	WHO Pre-qualified generic manufacturers[2]	Other countries of Production
Abacavir (ABC)	NRTI	Ziagen	GlaxoSmithKline		Argentina, India
Didanosine (DDI)	NRTI	Videx	Bristol Myers Squibb		Argentina, Brazil, India, Mexico, Thailand
Lamivudine (3TC)	NRTI	Epivir	GlaxoSmithKline	Cipla, India; Ranbaxy, India	Argentina, Brazil, India, Thailand
Stavudine (D4T)	NRTI	Zerit	Bristol Myers Squibb		Argentina, Brazil, India, Mexico, Thailand
Zalcitabine (DDC)	NRTI	Hivid	Roche		Argentina, Brazil, India
Zidovudine (AZT, ZDV)	NRTI	Retrovir	GlaxoSmithKline	Cipla, India; Combino Pharm SL, Spain; Ranbaxy, India	Argentina, Brazil, Canada, China, Colombia, India, Korea, Rep. of, Mexico, Spain, Thailand
Zidovudine + Lamivudine	NRTI	Combivir	GlaxoSmithKline	Ranbaxy, India	Argentina, Brazil, India, Thailand
Lamivudine + Stavudine	NRTI				India
Zidovudine + Lamivudine + Abacavir	NRTI	Trizivir	GlaxoSmithKline		
Tenofovir (TFV)	NtRTI	Viread	Gilead		
Delavirdine (DLV)	NNRTI	Rescriptor	Pfizer		India

Generic name	Class	Main brand®	Company[1]	WHO Pre-qualified generic manufacturers[2]	Other countries of Production
Efavirenz (EFV)	NNRTI	Sustiva; Stocrin	Bristol Myers Squibb		Argentina, India
Nevirapine (NVP)	NNRTI	Viramune	Boehringer Ingelheim	Cipla, India; Ranbaxy, India	Argentina, India, Thailand
Lamivudine + Stavudine + Nevirapine	2 NRTI + NNRTI				India, Thailand
Lamivudine + Zidovudine + Nevirapine	2 NRTI + NNRTI				India
Amprenavir (APV)	PI	Agenerase	GlaxoSmithKline		India
Indinavir (IDV)	PI	Crixivan	Merck		Argentina, India
Lopinavir/Ritonavir (LPV/r)	PI	Kaletra	Abbott		India
Nelfinavir (NFV)	PI	Viracept	Pfizer		Argentina, India
Ritonavir (RTV)	PI	Norvir	Abbott		India
Saquinavir – hard gel cps. (H-SQV)	PI	Invirase	Roche		India
Saquinavir – soft gel cps. (S-SQV or FTV)	PI	Fortovase	Roche		India

[1] Company: main manufacturing and/or marketing companies

[2] In the above Table, only generic manufacturers included in the WHO List of pre-qualified products have been listed. However, it has to be considered that many other manufacturers are producing antiretroviral drugs and many have applied to be included in the WHO List of pre-qualified products. A revision of the list occurs every two months, depending on updates so this list has to be considered subject to review. The updated complete list is available at the following website: http://www.who.int/medicines/organization/qsm/activities/pilotproc/pilotproc.shtml

NRTI Nucleoside Reverse Transcriptase Inhibitors

NtRTI Nucleotide Reverse Transcriptase Inhibitors

NNRTI Non-Nucleoside Reverse Transcriptase Inhibitors

PI Protease Inhibitor

USE OF ANTIRETROVIRAL DRUGS IN SPECIAL SITUATIONS

Generic name	Class	Paediatric approval	Use in pregnancy[1]	Recommended in persons with tuberculosis[3]
Abacavir (ABC)	NRTI	Yes	-	Yes
Didanosine (DDI)	NRTI	Yes	Yes	-
Lamivudine (3TC)	NRTI	Yes	**Yes**	Yes
Stavudine (D4T)	NRTI	Yes	Yes	-
Zalcitabine (DDC)	NRTI	No	-	-
Zidovudine (AZT, ZDV)	NRTI	Yes	**Yes**	Yes
Zidovudine + Lamivudine	NRTI	No	Yes	Yes
Zidovudine + Lamivudine + Abacavir	NRTI	No	-	Yes
Tenofovir (TFV)	NtRTI	No	-	-
Delavirdine (DLV)	NNRTI	No	-	-
Efavirenz (EFV)	NNRTI	Yes	No	Yes
Nevirapine (NVP)	NNRTI	Yes	**Yes**	Yes
Amprenavir (APV)	PI	Yes	-	-
Indinavir (IDV)	PI	No	Yes[2]	-
Lopinavir/Ritonavir (LPV/r)	PI	Yes	-	-
Nelfinavir (NFV)	PI	Yes	**Yes**	-
Ritonavir (RTV)	PI	Yes	Yes	-
Saquinavir – hard gel cps. (H-SQV)	PI	No	Yes[2]	Yes (only RTV- boosted)
Saquinavir – soft gel cps. (S-SQV or FTV)	PI	No	Yes[2]	Yes (only RTV- boosted)

NRTI Nucleoside Reverse Transcriptase Inhibitors
NtRTI Nucleotide Reverse Transcriptase Inhibitors
NNRTI Non-Nucleoside Reverse Transcriptase Inhibitors
PI Protease Inhibitors

1 When drugs are in bold and underlined, they are the first choice in their class for use in pregnancy. Refer to national guidelines or to the specific WHO Guidelines for the choice of the regimen/combination to be used in pregnant women. D4T + DDI combination should be avoided, because of the increased risk of fatal lactic acidosis/hepatic steatosis.

2 They should be used in pregnancy with RTV-boosted dosages, otherwise inadequate blood levels are obtained.

3 Refer to the special section on "Use of Antiretrovirals in Subjects with Tuberculosis"

ANTIRETROVIRALS INCLUDED IN THE WHO MODEL LIST OF ESSENTIAL MEDICINES

Abacavir (as sulfate) (ABC)	Tablet 300 mg; oral solution 100 mg/5 ml
Didanosine (DDI)	Tablet 25 mg, 100 mg, 150 mg, 200 mg
Lamivudine (3TC)	Tablet 150 mg; oral solution 50 mg/5 ml
Stavudine (D4T)	Capsule 15 mg, 20 mg, 30 mg, 40 mg; oral solution 5 mg/5 ml
Zidovudine (ZDV or AZT)	Capsule 100 mg, 250 mg, 300 mg; injection, 10 mg/ml in 20-ml vial; oral solution 50 mg/5 ml
Efavirenz (EFV or EFZ)	Capsule 50 mg, 100 mg, 200 mg
Nevirapine (NVP)	Tablet 200 mg; oral suspension 50 mg/5 ml
Indinavir (as sulfate) (IDV)[1]	Capsule 100 mg, 200 mg, 333 mg, 400 mg
Ritonavir (RTV, r)[2]	Capsule 100 mg; oral solution 400 mg/5 ml
Lopinavir + Ritonavir (LPV/r)[1]	Capsule 133.3 mg + 33.3 mg; oral solution, 400 mg/5 ml + 100 mg/5 ml
Nelfinavir (as mesylate) (NFV)	Tablet 250 mg; powder 50 mg/g
Saquinavir (SQV)[1]	Capsule (gel filled) 200 mg

[1] Not to be used as single Protease Inhibitors; recommended use in combination with boosting dose of Ritonavir.

[2] Ritonavir to be used only as "booster" for other Protease Inhibitors.

MODE OF ACTION OF ANTIRETROVIRAL DRUGS

Nucleoside Reverse Transcriptase Inhibitors (NRTI) and Nucleotide Reverse Transcriptase Inhibitors (NtRTI)

They act by incorporating themselves into the DNA of the virus (competing with natural nucleotides), thereby stopping the building process of transcription from RNA to DNA. The resulting DNA is incomplete and cannot create a new virus.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

They act by stopping HIV production by binding directly onto *reverse transcriptase* (non-competitively) and preventing the conversion of RNA to DNA.

Protease Inhibitors (PI)

They act by binding to the viral *protease*, in this way preventing the correct cleavage of viral proteins. Thus, they prevent HIV from being successfully assembled and released from the infected cells.

CHOICE OF ANTIRETROVIRAL DRUGS

The process of choosing the antiretroviral regimen is sometimes a complicated one and many aspects should be considered; however, no guidelines on treatment are being laid down; it is suggested that the respective national guidelines be referred to. With the exception of prevention of mother-to-child-transmission of HIV, any kind of antiretroviral mono- or dual therapy should be avoided.

In any case, a few combinations of antiretrovirals **should not be offered**, because of proved antagonism, suspect antagonism, overlapping toxicity profile and insufficient power.

The following combinations should not be offered because of antagonism:

- AZT + D4T
- DDC + 3TC

The following combinations should not be offered because of the overlapping toxicity profile:

- DDC + D4T
- DDC + DDI

WHO recommends that among PIs only Nelfinavir should be used as single PI, while Indinavir, Lopinavir and Saquinavir should be used in association with low doses of Ritonavir. The use of Ritonavir to increase plasma concentrations of other protease inhibitors (booster effect) has rapidly evolved from an investigational concept to widespread practice. Ritonavir increases plasma concentrations of other PIs by at least two mechanisms, including inhibition of gastrointestinal CYP450 during absorption, and metabolic inhibition of hepatic CYP450.

Standard doses of individual PIs result in trough drug levels that are often only slightly higher than the effective antiviral concentration; this may offer an opportunity for viral replication. In contrast, protease “boosting” or “enhancement” by Ritonavir

increases the trough levels of other protease inhibitors well above the IC_{50} or IC_{95}, minimizing opportunities for viral replication, and potentially allowing for drug activity even against moderately resistant strains of virus. In addition, these dual PI combinations often lead to more convenient regimens in terms of pill burden, scheduling and elimination of food restrictions. The addition of Ritonavir may also prevent Efavirenz or Nevirapine-induced drug interactions with the employed PI.

VIRAL RESISTANCE TO ANTIRETROVIRAL DRUGS

The high rate of replication that is found throughout the course of HIV infection and the variability of HIV, coupled with the relative inaccuracy of the enzyme HIV *reverse transcriptase*, are the main reasons for the frequent occurrence of copying errors in the transcription of viral genetic information. HIV replicates at the rate of around 10^8 to 10^{10} virus particles per day, probably giving raise daily to about $3x10^{-3}$ spontaneous changes (mutations) in its genetic sequence. The ultimate size of a viral population containing a mutation is probably determined by three concurrent factors: the forward mutation frequency, the replicative capability of the mutated virus and the "age" of the viral population containing the mutation i.e. how long ago this population was generated. With the on-going production of genetic variants of HIV, there is then a continuous selection for the "fittest" virus population.

Sub-optimal ART regimens that allow replication of HIV to continue in the presence of antiretroviral drugs encourage the growth of viral populations that are carrying a genetic mutation, which protects against these drugs. It is likely that many of these drug resistance mutations already exist before any antiretroviral drug is introduced and are further encouraged to proliferate under the selective pressure exerted by drug treatment.

Antiretroviral therapy can minimize the emergence of drug resistance in two ways:

- by maximizing and sustaining the suppression of viral replication.
- by using drugs where multiple mutations are required before resistance can occur.

Cross-resistance among the available classes of antiretroviral drugs is common and is an important consideration when assessing the possibility of sequencing (replacing one drug with another), should it become necessary to change a therapeutic regimen. Cross-

resistance implies that a population of virus resistant to one drug in a class is also resistant to other drugs of the same class. This is particularly liable to occur with the NNRTIs, especially if they are used as part of a regimen that produces incomplete suppression of viral replication.

A few drugs, namely Efavirenz, Lamivudine and Nevirapine present a very low "genetic barrier" to resistance because a single mutation is sufficient to produce resistance.

REASONS FOR AND INTERPRETATION OF DRUG INTERACTIONS

These Fact Sheets give an overview of current knowledge of drug interactions in which antiretrovirals are involved. In particular, PIs and NNRTIs tend to have complex metabolism and interactions, and - when given in combinations – they often affect each other's drug levels and potency. The knowledge of these combinations and interactions is a continuously evolving matter. Caution and close monitoring are advised when using combinations of PIs or PIs with NNRTIs. Treating physicians are strongly advised to verify all information with an HIV/AIDS specialist and check for any required dose adjustment with the same specialist or with an expert pharmacist.

Only modifications of at least 10% of drug concentrations reported by the manufacturer or by at least two different sources have been included in these Fact Sheets.

Many antiretroviral drugs, in particular NNRTI and PI classes are mainly metabolized in the liver and they can both inhibit or induct the cytochrome P450 system in one or more of its isoforms. This ends in a series of potential interactions at this level with other antiretroviral drugs or with different drugs that can be taken concurrently. A few interactions have been extensively studied, while others are only potential. For studied interactions, sometimes a dose modification in one or both the interacting drugs is needed or suggested. In this case, a note (**§** = dose modification of this drug is needed/suggested) is inserted in the text. For the exact necessary modification, please refer to a HIV/AIDS specialist, an expert pharmacist, information provided by the manufacturer, the most recent available indications published on peer-reviewed journals or selected websites. In case of interaction with methadone, no specific dose adjustment can be specified; dose of methadone should be adjusted in case of opioid withdrawal and increased till withdrawal symptoms disappear.

A few interactions can lead to significant and/or dangerous (sometimes life-threatening) modifications of the blood levels of one or both the involved drugs (possible increase in side effects and/or decreased efficacy of the involved drugs); in these cases, the co-administration of the two drugs is contraindicated. In other situations, the potential interaction could lead to potential significant and/or dangerous modifications of the blood levels of one or both the involved drugs (possible increase in side effects and/or decreased efficacy of the involved drugs), so caution is suggested if one of these drugs administered with the antiretroviral presented such interactions; furthermore, it is recommended that alternative drugs should be employed in this situation to prevent possible problems.

It is necessary to remind also that, as for any other new drug, unknown and previously unreported interactions can occur. Caution is necessary when using these drugs with others sharing a common metabolic pathway.

When adapting these Fact Sheets at the country level, it is strongly suggested to add all brand names marketed in the country, or at least the most used, to the generic name of the interacting drug.

DOSAGE

In case of renal impairment the dosage of a few antiretroviral drugs should be modified. In a few cases, a clear relationship between clearance of creatinine and the new dosage has been established.

Please refer to information provided by the manufacturer or on the most recent available indications published on peer-reviewed journals or on the selected web sites reported in this publication.

For a few protease inhibitors, the recommended WHO dosage is different from the one recommended by the manufacturer or the registered one. The choice of the WHO-recommended dosage is reported in the new WHO Guidelines "Scaling up Antiretroviral Therapy in Resource Limited Settings: Guidelines for a Public Health Approach" and is based on expert advice and with the intention to recommend effective and feasible regimens to be taken not more than twice daily.

DRUG HALF-LIFE

Reported half-life for each drug is relative to the use of the drug when administered without any interacting drug.

It is also advisable to not interpret it for modifying the recommended dosage or schedule of administration during the day. For example, Didanosine only has a plasma half-life of 1.5 ± 0.4 hours, but it is the longer intracellular half-life that permits twice daily dosing.

USE OF ANTIRETROVIRALS IN SUBJECTS WITH TUBERCULOSIS

WHO recommends that people with TB/HIV complete their TB therapy prior to beginning ARV treatment, unless there is a high risk of HIV disease progression and death during the period of TB treatment (i.e., a CD4 count $<200/mm^3$ or the presence of disseminated TB). In cases where a person needs TB and HIV treatment concurrently, first line treatment options include ZDV/3TC or D4T/3TC plus either an NNRTI or ABC. If an NNRTI-based regimen is used, EFV would be the preferred drug, as its potential to aggravate the hepatotoxicity of TB treatment appears less than with NVP and because of the potential for clinically significant interactions with Rifampicin. However, EFV dosage needs to be increased to 800 mg/day. Except for SQV/r, PIs are not recommended during TB treatment with Rifampicin due to their interactions with the latter drug.

Antiretroviral therapy for individuals with tuberculosis coinfection

Situation	Recommendations
Pulmonary TB and CD4 count $<50/mm^3$ or extrapulmonary TB	Start TB therapy. Start one of these regimens as soon as TB therapy is tolerated: ZDV/3TC/ABC ZDV/3TC/EFV ZDV/3TC/SQV/r ZDV/3TC/NVP
Pulmonary TB and CD4 50-200/mm^3 or total lymphocyte count <1000-$1200/mm^3$	Start TB therapy. Start one of these regimens after 2 months of TB therapy: ZDV/3TC/ABC ZDV/3TC/EFZ ZDV/3TC/SQVr ZDV/3TC/NVP
Pulmonary TB and CD4 $>200/mm^3$ or total lymphocyte count >1000-$1200/mm^3$	Treat TB. Monitor CD4 counts if available. Start ART according to guidelines

INTERPRETATION OF DRUG-RELATED SIDE EFFECTS

The causes of any new symptoms or signs developing after the initiation of antiretroviral therapy should be identified whenever possible. New symptoms may be related to intercurrent illness or due to adverse effects of antiretroviral drugs. Shortly after commencing the treatment, certain opportunistic infections may become clinically apparent as a result of the syndrome of immune reactivation, and these should be diagnosed and treated.

If new complaints are due to adverse effects of drugs, these should be explained to the patient and appropriate measures implemented, by: (i) adapting the drug regimen, (ii) providing symptomatic treatment or (iii) giving simple reassurance.

Direct questioning on early symptoms of the documented clinically serious adverse effects of antiretroviral drugs is mandatory, as is systematic physical and laboratory examination to look for indicative signs. In this way, adverse effects like severe anaemia and neutropenia, polyneuritis, pancreatitis, hepatitis, nephrolithiasis and serious hypersensitivity dermatitis can be detected early and remedial actions taken.

In order to obtain better compliance to the treatment, patients should be told of the possible occurrence of side effects before starting antiretroviral drugs. This patient education will reinforce the acceptability of minor and/or transient side effects.

The drug-related side effects listed in these Fact Sheets are not exhaustive of all the side effects reported during treatment with each drug. The included side effects have been chosen because of frequency of report, their severity, and of high correlation with the corresponding drug. Any new, unexpected and previously unreported side effects should be reported as soon as possible to the competent national authority.

Class side effects are listed separately from the sections relating to the single drugs.

The management of the most frequent or serious side effects associated with antiretrovirals are shown in the tables below.

Frequency	
< 1%	-
1%	+/-
1.1 – 5%	+
5.1 - 19.9%	+ +
20% or more	+ + +
Severity	
Generally mild	+/-
Mainly mild to moderate	+
Moderate or rarely severe	+ +
Frequently severe	+ + +
Can be life-threatening	☠

Clinical signs, symptoms and management of symptoms of serious adverse effects of antiretroviral drugs that require drug discontinuation

Adverse effect	Possible offending drug(s)	Clinical signs / symptoms	Management
Acute hepatitis	NVP; EFV less common; more uncommon with ZDV, DDI, D4T and protease inhibitors, most frequently with RTV	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	If possible, monitor serum transaminases, bilirubin. All ARVs should be stopped until symptoms resolve. NVP should be permanently discontinued.

Adverse effect	Possible offending drug(s)	Clinical signs / symptoms	Management
Acute pancreatitis	DDI, D4T; 3TC (infrequent)	Nausea, vomiting, and abdominal pain	If possible, monitor serum pancreatic amylase, lipase. All ART should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., ZDV, ABC).
Lactic acidosis	All NRTIs	Initial symptoms are variable: a clinical prodromal syndrome may include generalized fatigue and weakness, gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss), respiratory symptoms (tachypnea and dyspnea) or neurological symptoms (including motor weakness).	Discontinue all ARVs; symptoms may continue or worsen after discontinuation of ART. Administer supportive therapy. Regimens that can be considered for restarting ART include a PI combined with NNRTI and possibly either ABC or TFV
Hypersensitivity reaction	ABC; NVP	ABC: Constellation of symptoms including: fever, fatigue, myalgia, nausea/vomiting, diarrhoea, abdominal pain, pharyngitis,	Stop all ARVs until symptoms resolve. The reaction progressively worsens with continued drug administration and can

Adverse effect	Possible offending drug(s)	Clinical signs / symptoms	Management
		cough, dyspnea (with or without rash). While these symptoms overlap those of common infectious illnesses, the combination of acute onset of both respiratory and gastrointestinal symptoms after starting ABC is more typical of a hypersensitivity reaction. NVP: Systemic symptoms of fever myalgia, arthralgia, hepatitis, eosinophilia with or without rash.	be fatal. Administer supportive therapy. Do not rechallenge with ABC (or NVP), as anaphylactic reactions and death have been reported. Once symptoms resolve, restart ARVs with change to different NRTI if ABC-associated or to a PI- or NRTI-based regimen if NVP-associated.
Severe rash/Stevens-Johnson syndrome (SJS)	NNRTIs: NVP, EFV	Rash usually occurs during the first 2-4 weeks of treatment. The rash is usually erythematous, maculopapular, confluent, most prominent on the body and arms, may be pruritic and can occur with or without fever. Life-threatening Stevens-Johnson Syndrome or toxic epidermal necrolysis (SJS/TEN) has been reported in ~0.3% of infected individuals receiving NVP.	Discontinue all ARVs. Permanently discontinue NVP for rash with systemic symptoms such as fever, severe rash with mucosal lesions or urticaria, or SJS/TEN; once resolved, switch ART regimen to different ARV class (e.g., 3 NRTIs or 2 NRTIs and PI). If rash is moderate but not severe and without mucosal or systemic symptoms, change in NNRTI (e.g., NVP to EFV) could be considered after rash resolves.

Adverse effect	Possible offending drug(s)	Clinical signs / symptoms	Management
Severe peripheral neuropathy	DDI, D4T, 3TC	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can be observed.	Stop suspect NRTI. Switch to different NRTI that does not have neurotoxicity (e.g., ZDV, ABC). Symptoms usually resolve within 2-3 weeks from discontinuation.

Management of selected adverse effects of antiretroviral drugs that usually do not require drug discontinuation

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms or laboratory investigations	Management
Anaemia	ZDV	Regular laboratory monitoring	In case of severe anaemia, replace ZDV or reduce dosage if it cannot be replaced. Transfusion may be required.
Diarrhoea	DDI, ZDV, APV, LPV, NFV, RTV, SQV; less frequently: IDV, DLV, EFV, ABC, 3TC, D4T, DDC	It occurs almost invariably in the first weeks of treatment. It is frequently mild and self-limited. In a limited number of cases, it can be more severe with dehydration or can last longer.	If mild, one should wait for spontaneous resolution and/or treat symptomatically with loperamide, calcium carbonate, psyllium, oat bran. If severe, rehydrate and treat symptomatically. It rarely leads to discontinuation of the responsible drug.

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms or laboratory investigations	Management
Gastrointestinal symptoms (other than diarrhoea)	ABC, DDI, DDC, ZDV, TFV, DLV, NVP, APV, LPV, RTV, SQV; less frequently: 3TC, D4T, IDV, NFV	They occur most frequently in the first weeks of treatment. They are frequently self-limited.	They can be treated symptomatically. They rarely lead to discontinuation of the responsible drug.
Hepatitis	NVP; EFV less common; more uncommon with ZDV, DDI, D4T (<1%); and protease inhibitors, most frequently with RTV	Jaundice, liver enlargement, gastrointestinal symptoms, fatigue, anorexia; NVP-associated hepatitis may have hypersensitivity component (drug rash, systemic symptoms, eosinophilia)	Monitor serum transaminases and bilirubin. Discontinue therapy if confirmed. NVP should be permanently discontinued.
Hepatitis B	3TC	3TC has a potential efficacy for hepatitis B infection, so hepatitis flare up can happen if and when 3TC is discontinued	Usually self-limiting. Monitor patients and do not administer ARVs with potential liver toxicity before resolution.
Nephrolithiasis (recurrent in 50%)	IDV	Crystalluria, hematuria, flank pain	Possibly, temporarily discontinue IDV, increase hydration. Treat pain symptomatically. Restart after the episode resolves
Neutropenia	ZDV in particular, but also 3TC, IDV, TFV	Regular laboratory monitoring	If absolute neutrophil count is < 500/ml, replace ZDV or reduce dosage if it cannot be replaced (other drugs need to be replaced)
Pancreatitis	DDI, D4T; 3TC (infrequent)	Nausea, vomiting, and abdominal pain request evaluation for pancreatitis	Evaluate serum pancreatic amylase and lipases. Discontinue therapy if confirmed. All ART

Adverse effect	Possible offending drug(s)	Clinical signs/symptoms or laboratory investigations	Management
			should be stopped until symptoms resolve. Restart ART with change to different NRTI, preferably one without pancreatic toxicity (e.g., ZDV, ABC).
Peripheral neuropathy	DDI, D4T, 3TC	Pain, tingling, numbness of hands or feet; distal sensory loss, mild muscle weakness, and areflexia can occur.	Stop suspect NRTI. Switch to different NRTI that does not have neurotoxicity (e.g., ZDV, ABC). Symptoms usually resolve within 2-3 weeks from discontinuation.

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTIs)

Abacavir (ABC)

Class

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Available formulations

- Oral solution: 20 mg/ml
- Tablets: 300 mg

Storage

Room temperature

Dose (WHO recommended)

Adults:	300 mg (2 tabs.) twice daily
Children:	8 mg/kg every 12 hours (with a maximum of 300 mg per dose) (over age 3 months)

Food effect

It can be taken with or without food.

Half-life in plasma

1.54 ± 0.63 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Rare
- Abacavir levels are increased by alcohol (care must be taken when co-administered with Ritonavir or Lopinavir oral solutions in children).
- Abacavir increases levels of **§**Amprenavir.
- Abacavir decreases levels of **§**Methadone (in some patients).

Side Effects	Frequency	Severity
Nausea	+ + +	+/-
Vomiting	+ + +	+/-
Fever	+ +	+/-
Triglycerides elevation	+ +	+/-
Hypersensitivity reaction*	+	☠

Side Effects	Frequency	Severity
Headache	+	+/-
Loss of appetite	+	+/-
Fatigue	+	+/-
Insomnia and other sleep disorders	+	+/-
Increase in creatine phosphokinase	+/-	+/-
Diarrhoea	+/-	+/-
Pancreatitis	-	+ +/+ + +

Note* It is rare (2-5%), but it can be fatal. It usually appears during the first six weeks of treatment with Abacavir. It can be diagnosed in the presence of a rash or two or more of the following symptoms: fever, GI symptoms (nausea, vomiting, diarrhoea, abdominal pain), fatigue, malaise, anorexia, respiratory symptoms (sore throat, cough, shortness of breath, dyspnea). Patients who develop signs or symptoms of hypersensitivity should discontinue Abacavir as soon as hypersensitivity reaction is suspected; they must never take again Abacavir, because more severe symptoms may recur within hours.

Didanosine (DDI)

Class

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Available formulations

- Buffered powder for oral solution: 2, 4 g (for children); final concentration: 10 mg/ml
- Buffered powder for oral solution: 100, 167, 250 mg (single doses for adults)
- Chewable/dispersible buffered tablets: 25, 50, 100, 150, 200 mg (at least 2 tabs. should be administered each time to ensure adequate buffering capacity)
- Enteric coated (EC) capsules: 125, 200, 250, 400 mg

Storage

- Room temperature for tablets and capsules.
- Reconstituted buffered powder should be refrigerated; oral solution for children is stable after reconstitution for 30 days if refrigerated.

Dose (WHO recommended)

Adults:	**> 60 kg**: 200 mg (buff. tabs.) twice daily or 250 mg (buff. powder) twice daily or 400 mg once daily (buff. tabs. or EC caps.)
	< 60 kg: 125 mg (buff. tabs.) twice daily or 167 mg (buff. powder) twice daily or 250 mg once daily (buff. tabs. or EC caps.)
Children:	**< 3 months**: 50 mg/m^2 of body surface twice daily or 240 mg/m^2 once daily
	3 months - < 13 years: 90 mg/m2 twice daily or 240 mg/m2 once daily
	= 13 years or > 60 kg = adult dosage

Food effect

It should be taken on empty stomach; at least ½ hour before or two hours after meal.

Half-life in plasma

1.5 ± 0.4 hours

Interactions with other drugs

- Rare
- Contraindicated drugs (DDI not to be taken with these drugs): Allopurinol.
- Didanosine levels are decreased by Methadone (**§**DDI).
- Didanosine levels are increased by oral Ganciclovir (**§**DDI); Tenofovir.
- Didanosine* decreases absorption of Delavirdine; Indinavir (at least one hour before or two hours after Didanosine on an empty stomach); Ritonavir (at least two hours before or after Didanosine); fluoroquinolones.

* Didanosine in the form of tablets or paediatric powder

- Didanosine* can possibly decrease absorption of Dapsone; Itraconazole; Ketoconazole (separate administration: at least two hours before or after Didanosine).

Side Effects	Frequency	Severity
Pancreatitis#	+ +	☠
Peripheral neuropathy	+ +	+ + +
Increase in liver function tests	+ +	+
Diarrhoea	+ +	+/-
Nausea	+ +	+/-
Elevated amylase	+	+ +
Elevated lipase	+	+
Vomiting	+	+/-
Rash	+	+/-
Elevated urate	+	+/-
Headache	+	+/-
Abdominal pain	+/-	+/-

The risk is increased by the concomitant use of D4T or D4T + Hydroxyurea

Lamivudine (3TC)

Class

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Available formulations

- Oral suspension: 10 mg/ml
- Tablets: 150, 300 mg

Storage

Room temperature

Dose (WHO recommended)

Adults:	**> 60 kg**: 200 mg (buff. tabs.) twice daily or 250 mg (buff. powder) twice daily or 400 mg once daily (buff. tabs. or EC caps.)
	< 60 kg: 125 mg (buff. tabs.) twice daily or 167 mg (buff. powder) twice daily or 250 mg once daily (buff. tabs. or EC caps.)
Children:	**< 3 months**: 50 mg/m^2 of body surface twice daily or 240 mg/m^2 once daily
	3 months - < 13 years: 90 mg/m2 twice daily or 240 mg/m2 once daily
	= 13 years or > 60 kg = adult dosage

Food effect

It can be taken with or without food.

Half-life in plasma

From 5 to 7 hours

Metabolism

It is eliminated unchanged through renal excretion.

Interactions with other drugs

- Rare
- Trimethoprim/Sulfamethoxazole (TMP/SMX) increases Lamivudine blood levels.
- Do not administer with Zalcitabine due to possible antagonism.

Side Effects	Frequency	Severity
Headache	+ +	+/-
Neutropenia	+	+ +
Nausea	+	+/-
Increase in liver function tests	+	+/-
Skin rash	+	+/-

Side Effects	Frequency	Severity
Fatigue	+	+/-
Loss of appetite	+	+/-
Mood disorders	+/-	+
Diarrhoea	+/-	+/-
Abdominal pain/cramps	+/-	+/-
Cough	+/-	+/-
Pancreatitis	-	+ + +

Stavudine (D4T)

Class

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Available formulations

- Oral solution: 1 mg/ml
- Capsules: 15, 20, 30 and 40 mg

Storage

Room temperature. After reconstitution, oral solution should be kept refrigerated; if so, it is stable for 30 days.

Dose (WHO recommended)

Adults: **< 60 kg**: 30 mg (1 caps.) twice dauly
= 60 kg: o40 mg (1 caps.) twice daily

Children: 1 mg/kg: every 12 hours (if at laeast 30 kg: same as adults)

Food effect

It can be taken with or without food.

Half-life in plasma

0.96 ± 0.26 hours

Interactions with other drugs

- Rare
- Stavudine levels are decreased by Methadone.
- Do not administer with Zidovudine due to antagonism.

Side Effects	Frequency	Severity
Peripheral neuropathy#	+ or + + +	+ + +
Increase in liver enzymes	+ + +	+
Headache	+ +	+
Pancreatitis*	+	☠
Increase in amylase	+	+ + +
Increase in lipids	+	+
Increase in urate	+	+/-
Increase in creatine phosphokinase	+	+/-
GI disturbances	+	+/-
Rash	+	+/-

Observed in up to 24% patients with less than 50 CD4/mm^3

* The risk is increased by the concomitant use of DDI or DDI + Hydroxyurea.

Zalcitabine (DDC)

Class

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Available formulations

Tablets: 0.375 and 0.75 mg

Storage

Room temperature

Dose

Adults:	0.75 mg (1 tab.) three times daily
Children:	0.01 mg/kg every eight hours (paediatric use not approved)

Food effect

It can be taken with or without food; high fat meal should be avoided.

Half life in plasma

From 1.2 to 2 hours.

Interactions with other drugs

- Antiacids decrease the absorption of Zalcitabine.
- Concomitant use of Didanosine or of Pentamidine increases the risk of pancreatitis.
- Do not administer with Lamivudine due to possible antagonism.
- Do not administer with Ribavirine due to *in vitro* antagonism.
- Probenecid decreases renal secretion of DDC: modify dose of DDC.

Side Effects	Frequency	Severity
Peripheral neuropathy	+ + +	+ + +
Stomatitis and oral ulcers	+ +	+ + +
GI disturbances	+ +	+/-
Pancreatitis	+	+ + +
Increase in liver function tests	+	+
Headache	+	+/-
Fatigue	+	+/-

Zidovudine (AZT, ZDV)

Class

Nucleoside Reverse Transcriptase Inhibitor (NRTI)

Available formulations

- Oral solution: 10 mg/ml

- Capsules: 100 and 250 mg
- Tablets: 300 mg
- IV solution: 10 mg/ml (only use in special circumstances)

Storage

Room temperature

Dose

Adults:	200 mg (2 x 100-mg caps.) three times daily or 300 mg (1 tab.) twice daily or 250 mg (1 x 250-mg cap.) twice daily
Children:	**WHO recommended**:
	< 4 weeks: 4 mg/kg twice daily
	4 weeks - < 13 years: 180 mg/m^2 of body surface twice daily
	[Also possible: 90-180 mg/m^2 every 6-8 hours (480 mg/m^2 daily to a maximum of 600 mg daily)]

Food effect

It can be taken with or without food.

Half-life in plasma

From 0.5 to 3 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Increased toxicity can be observed with concomitant administration of Acyclovir; Gancyclovir; Interferon alpha; Trimethoprim/Sulfamethoxazole (TMP/SMX) and other drugs causing bone marrow suppression.
- Zidovudine levels may be increased by Atovaquone; Fluconazole; Methadone; Probenecid and Valproic acid.
- Zidovudine levels may be decreased by Clarithromycin (interference with absorption); Nelfinavir; Rifampicin and Ritonavir.

- Ribavirin decreases the intracellular phosphorilation of Zidovudine (activation); concomitant use should be avoided.
- Antagonism with Stavudine and with Doxorubicin (do not co-administer)

Side Effects	Frequency	Severity
GI intolerance	+ + +	+/-
Headache	+ +	+/-
Asthenia/malaise	+ +	+/-
Anorexia	+ +	+/-
Increase in liver function tests	+	+
Anaemia	+/-	+ + +
Insomnia	+/-	+/-
Neutropenia	-	+ + +
Myopathy and myositis	- (long-term use)	+ + +
Bluish colouration of nails	-	+/-

Class Adverse Drug Reactions to Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Lactic Acidosis/Hepatic Steatosis

The occurrence of lactic acidosis and severe hepatomegaly with steatosis during the use of NRTIs appears to occur at a low frequency, but with a high fatality risk. The incidence of lactic acidosis seems to be around 1‰, while simple elevation in serum lactate levels can be found in as many as 5-21% patients treated with NRTI-containing regimens. While uncommon, lactic acidosis is associated with a high fatality rate (33-57%). Risk factors include female gender, high body mass index, prolonged NRTI use, and possibly pregnancy, acquired riboflavin and thiamine deficiency, and D4T use. Cases have occurred as soon as one month and as late as 20 months after starting therapy. The initial clinical manifestations of lactic acidosis are variable and may include non-specific gastrointestinal symptoms (weight loss, anorexia, nausea, vomiting, abdominal pain, diarrhoea) without dramatic elevation of hepatic enzymes, and in some case dyspnea and/or fatigue. Evaluation shows lactic acidosis with possibly elevated CPK, ALT, and/or LDH, low bicarbonate and increased anion gap. Abdominal CT scans or liver biopsy often show steatosis.

Fatalities have been reported despite intensive supportive treatment; in other cases, the adverse event has resolved after discontinuation of NRTIs.

All NRTIs have been implicated, although some studies suggest higher rates with the use of D4T or DDI/Hydroxyurea.

The most important therapeutic intervention appears to be NRTI withdrawal; the safety of substituting alternative drugs in this class is not known.

This adverse event has been attributed to mitochondrial toxicity caused by NRTIs. Furthermore, it is possible that other clinical expressions of mitochondrial toxicity include myopathy (AZT-related), dilated cardiomyopathy (AZT), peripheral neuropathy (D4T, DDI, DDC), pancreatitis (DDI, D4T, 3TC), asthenia, bone marrow suppression (AZT) and/or lipoatrophy (D4T, AZT, DDI).

Liver toxicity manifested as asymptomatic increases in liver transaminases, with normal bilirubinaemia, occurs in 5-15% of patients receiving NRTIs, but hepatitis is more uncommon, seen in <1%; hepatitis has been reported with all NRTIs except 3TC and ABC. NRTI-associated liver toxicity with hepatic steatosis usually is not seen until after more than six months of therapy.

NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NtRTIs)

Tenofovir (TFV)

Class

Nucleotide Reverse Transcriptase Inhibitors (NtRTI)

Available formulations

Tablets: 300 mg

Storage

Room temperature

Dose

Adults: 300 mg (1 tab.) once daily

Food effect

It should be taken with a meal.

Metabolism

Eliminated mainly unchanged in the urine.

Half life in plasma

17 hours

Interactions with other drugs

- Yes; minimal inhibition of CYP1A (Cytochrome P450 1A isoform)
- If Didanosine or antiacids are administered, they should be taken at least two hours apart.
- Tenofovir levels are increased by Lopinavir/r.
- Tenofovir increases levels of Didanosine.
- Tenofovir decreases levels of Lopinavir and Ritonavir.

Care

Tenofovir should not be administered to patients with renal insufficiency (patients with creatinine clearance < 60 ml/min)

Side Effects	Frequency	Severity
Nausea	+ +	+
Diarrhoea	+ +	+
Vomiting	+	+
Anorexia	+	+
Increase in liver function tests	+	+
Flatulence	+	+/-
Headache	+	+/-
Neutropenia	+/-	+ +

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

Delavirdine (DLV)

Class

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

Available formulations

Tablets: 100 and 200 mg

Storage

Room temperature

Dose

Adults: 400 mg (2 x 200-mg tabs.) three times daily

Children: Paediatric use not approved

If difficulties in swallowing are encountered, 100-mg tabs can be dispersed in water to produce slurry.

Food effect

It can be taken with or without food.

Half life in plasma

5.8 hours (from 2 to 11).

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; inhibition of CYP3A4 (Cytochrome P450 3A4 isoform)
- If Didanosine or antiacids are administered, they should be taken at least one hour apart.

- Contraindicated drugs (DLV not to be taken with these drugs): Alprazolam; Astemizole; Cisapride; Ergotamine and similar alkaloids; Garlic supplements; H-2 blockers; Lovastatin; Midazolam; proton pump inhibitors; Rifabutin; Rifampicin; Simvastatin; St. John's wort *(hypericum perforatum)*; Terfenadine and Triazolam.
- Delavirdine levels are increased by Clarithromycin and Fluoxetine.
- Delavirdine levels are decreased by Nelfinavir; Rifampicin and Rifabutin.
- Delavirdine increases levels of Amprenavir; Clarithromycin; Dapsone; **§**Indinavir; Nelfinavir; Quinidine; Rifabutin; Ritonavir; **§**Saquinavir; **§**Sildenafil and Warfarin.
- Potential interactions with anticonvulsants; statins; Methadone; oral contraceptives; Calcium channel blockers and oral anticoagulants.

Side Effects	Frequency	Severity
Rash*	+ + +	+ +
Nausea	+ +	+/-
Severe rash*	+	+ + +
Vomiting	+	+/-
Elevated transaminase	+	+/-
Diarrhoea	+	+/-
Fatigue	+/-	+/-
Headache	+/-	+/-
Stevens-Johnson syndrome	- (<1%)	☠

* In up to 4.3% of patients in clinical trials, it caused interruption of treatment.

Efavirenz (EFV)

Class

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

Available formulations

- Capsules: 50, 100, 200 and 600 mg
- Syrup: 30 mg/ml (it requires higher doses)

Storage

Room temperature

Dose (WHO recommended)

Adults: 600 mg (1 x 600 mg caps. or 3 x 200-mg caps.) once daily

Children: Depending on weight – see table below

It is usually taken before sleep to reduce CNS adverse events; in case of persistence of symptoms, dose can be divided in two administrations.

Weight	Paediatric Dose
From 10 to < 15 kg	200 mg (caps.) 270 mg (syrup)
From 15 to < 20 kg	250 mg (caps.) 300 mg (syrup)
From 20 to < 25 kg	300 mg (caps.) 360 mg (syrup)
From 25 to < 32.5 kg	350 mg (caps.) 450 mg (syrup)
From 32.5 to < 40 kg	400 mg (caps.) 510 mg (syrup)
> 40 kg	600 mg

Food effect

It can be taken with or without food; high fat meal should be avoided.

Half-life in plasma

From 52 to 76 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; inhibition and induction of CYP3A4 (Cytochrome P450 3A4 isoform)

- Contraindicated drugs (EFV not to be taken with these drugs): Astemizole; Cisapride; Clarithromycin; Ergotamine and similar alkaloids; Garlic supplements; Midazolam; St. John's wort *(hypericum perforatum)*; Terfenadine and Triazolam.
- Efavirenz levels are increased by Ritonavir.
- Efavirenz levels are decreased by Rifampicin (**§**EFV) and Saquinavir.
- Efavirenz increases levels of Nelfinavir and Ritonavir.
- Efavirenz decreases levels of **§**Amprenavir; Clarithromycin; **§**Indinavir; **§**Lopinavir; **§**Methadone; **§**Rifabutin and Saquinavir.
- Potential interactions with anticonvulsants; statins; oral contraceptives; tricyclic antidepressant and oral anticoagulants.

Side Effects	Frequency	Severity
Rash[1]	+ + + (in up to 25-40% of patients)	+ +
CNS symptoms[2]	+ + +	+ +
Elevated transaminase	+ +	+
Severe rash[1]	+	+ + +
Severe CNS symptoms[2]	+	☠
Diarrhoea	+	+/-
Stevens-Johnson syndrome	- (0.1%)	☠

[1] In up to 1.7% of patients in clinical trials, it caused discontinuation of treatment. Rash of any grade of severity is more frequent in children.

[2] CNS symptoms include: dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria; they are present in up to 50% of patients taking Efavirenz. Usually, these symptoms spontaneously disappear over 2-4 weeks; but in up to 2.6% of patients they cause interruption of treatment. Patients with a history of psychiatric disorders appear to be at greater risk of serious psychiatric adverse experiences, with the frequency of each of the above events ranging from 0.3% for mania reactions to 2% for both severe depression and suicidal ideation. Patients receiving EFV should be alerted to the potential for additive central nervous system effects when EFV is used concomitantly with alcohol or psychoactive drugs.

Nevirapine (NVP)

Class

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

Available formulations

- Oral suspension: 10 mg/ml
- Tablets: 200 mg

Storage

Room temperature

Dose

Adults: 200 mg (1 tabs.) twice daily (200 mg once daily for the first 14 days) **(WHO recommended)**

Children: **WHO recommended**

15-30 days: 5 mg/kg once daily for the first 14 days, then 120 mg/kg/m^2 of body surface twice daily for 14 days, then 200 mg/kg/m^2 twice daily

30 days - 13 years: 120 mg/kg/m^2 twice daily for the first 14 days, then 200 mg/kg/m^2 twice daily

or **2 months - 8 years**: 4 mg/kg once daily for the first 14 days, then 7 mg/kg twice daily

> 8 years: 4 mg/kg once daily for the first 14 days, then 4 mg/kg twice daily (total dose not exceeding 400 mg daily for any patient)

Starting treatment with a reduced dose is necessary because during the first two weeks of treatment NVP induces its own metabolism. This also decreases the risk of rash and early NVP-induced hepatitis.

Food effect

It can be taken with or without food.

Half-life in plasma

From 25 to 30 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; induction of CYP3A4 (Cytochrome P450 3A4 isoform)
- Contraindicated drugs (NVP not to be taken with these drugs): Ketoconazole; Garlic supplements and St. John's wort (*hypericum perforatum*).
- Nevirapine levels are increased by Cimetidine; Clarithromycin and Indinavir.
- Nevirapine levels are decreased by Rifampicin and Rifabutin.
- Nevirapine decreases levels of Clarithromycin; **§**Indinavir; **§**Lopinavir; **§**Methadone; Ritonavir and Saquinavir (to be given together only if co-administered with RTV);

Potential interactions with anticonvulsants; statins; oral contraceptives; tricyclic antidepressants and oral anticoagulants.

Side Effects	Frequency	Severity
Rash*	+ + +	+ +
Severe rash*	+ +	+ + +
Nausea	+ +	+/-
Headache	+	+/-
Fatigue	+	+/-
Elevated transaminase	+	+/-
Hepatitis/hepatic failure	+/-	+ + +
Stevens-Johnson syndrome	- (<1%)	☠

* In up to 7% of patients in clinical trials, rash caused interruption of treatment.

PROTEASE INHIBITORS (PIs)

Amprenavir (APV)

Class

Protease Inhibitor (PI)

Available formulations

- Oral suspension: 15 mg/ml
- Capsules: 50 and 150 mg

Storage

Room temperature

Dose

Adults:	1200 mg (8 caps.) twice daily
	If given with Ritonavir boosting dose:
	600 mg (4 caps.) APV + 100 mg (1 caps.) RTV twice daily
	1200 mg (8 caps.) APV + 200 (2 caps.) mg RTV once daily
Children:	capsules: 20 mg/kg every 12 hours or 15 mg/kg three times daily (total dosage should not exceed a total of 1200 mg every 12 hours)
	oral solution: 22.5 mg/kg every 12 hours or 17 mg/kg three times daily total dosage should not exceed a total of 1400 mg every 12 hours) (see warning below)

Amprenavir is 14% less bioavailable from the liquid formulation than from the capsules; therefore Amprenavir capsules and Amprenavir oral solution are not interchangeable on a milligram-per-milligram basis.

Food effect

It can be taken with or without food; high fat meal should be avoided.

Half-life in plasma

From 7.1 to 10.6 hours

Metabolism

Mainly in the liver

Warning

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, Amprenavir oral solution is contraindicated in infants and children below the age of four years, pregnant women, patients with hepatic or renal failure. Certain ethnic populations, such as Asians, Eskimos, and Native Americans, may be at increased risk of propylene glycol-associated adverse events because of alcohol dehydrogenase polymorphisms; however, no data are available on propylene glycol metabolism in these groups.

Interactions with other drugs

- Yes; inhibition of CYP3A4 (Cytochrome P450 3A4 isoform)
- If Didanosine or antacids are administered, they should be taken at least one hour apart.
- Contraindicated drugs (APV not to be taken with these drugs): Astemizole; Bepridil; Cisapride; Ergotamine and similar alkaloids; Garlic supplements; Lovastatin; Midazolam; Pimozide, Rifampicin; St. John's wort *(hypericum perforatum)*; Simvastatin; Terfenadine and Triazolam.
- Because of the large amount of the excipient propylene glycol, Amprenavir oral solution should not be co-administered with Disulfiram or Metronidazole or some cephalosporins, such as Cefamandole or Cefoperazone.
- Amprenavir levels are increased by Abacavir (**§**APV); Delavirdine; Clarithromycin; Indinavir; Ketoconazole; Lopinavir; Nelfinavir; **§**Ritonavir (**§**APV) and Zidovudine.
- Amprenavir levels are decreased by Dexamethasone; Efavirenz (**§**APV); **§**Lopinavir (**§**APV); Nelfinavir; Nevirapine; Rifampicin; **§**Rifabutin and Saquinavir.

- Amprenavir increases levels of Carbamazepine; Clarithromycin; Itraconazole; Ketoconazole; **§**Rifabutin; **§**Sildenafil and Zidovudine.
- Amprenavir decreases levels of Indinavir; **§**Lopinavir (**§**APV) and Saquinavir
- Potential interactions with anticonvulsants; benzodiazepins; Calcium channel blockers; statins; oral contraceptives; tricyclic antidepressants; oral anticoagulants; Amiodarone; Methadone; Quinidine and immunosuppressants.

Side Effects	Frequency	Severity
Rash	+ + + (in up to 20-25% of patients)	+ +
Diarrhoea or loose stools	+ + +	+/-
Nausea	+ + +	+/-
Paresthesias (perioral or peripheral)	+ + + (10-30%)	+/-
Vomiting	+ + +	+/-
Taste disorders	+ +	+/-
Depressive or mood disorders	+ +	+/-
Fatigue	+	+/-
Increase in liver function tests	+	+/-
Stevens-Johnson syndrome	+/- (up to 1%)	☠
Headache	+/-	+/-

Indinavir (IDV)

Class

Protease Inhibitor (PI)

Available formulations

Capsules: 100, 200, 333 and 400 mg

Storage

Room temperature; in original container containing desiccant

Dose

Adults: 800 mg (2 x 400 mg caps.) IDV + 100 mg (1 caps.) RTV twice daily **(WHO recommended)**

Also possible: 800 mg (2 x 400-mg caps.) every 8 hours

Children: Paediatric use not approved

Consistent daily intake of liquids is needed (at least 1.5 litres of liquids every 24 hours)

Food effect

It should be taken on empty stomach (low fat snack allowed); possibly 1 hour before or 2 hours after meals.

Half-life in plasma

1.8 ± 0.4 hours

Metabolism

Mainly in the liver; less than 20% eliminated unchanged in the urine.

Interactions with other drugs

- Yes; inhibition of CYP3A4 (Cytochrome P450 3A4 isoform)
- If Didanosine or antiacids are administered, they should be taken at least one hour apart.
- Contraindicated drugs (IDV not to be taken with these drugs): Astemizole; Atorvastatin; Cisapride; Ergotamine and similar alkaloids; Garlic supplements; Lovastatin; Midazolam; Pimozide; Rifampicin; Saquinavir (*in vitro* antagonism); Simvastatin; St. John's wort *(hypericum perforatum)*; Terfenadine and Triazolam.

- Indinavir levels are increased by Clarithromycin; Delavirdine (**§**IDV); Ketoconazole (**§**IDV); Itraconazole (**§**IDV); Lopinavir/r (**§**IDV); Nelfinavir; Quinidine; **§**Ritonavir (**§**IDV) and Sildenafil.
- Indinavir levels are decreased by Amprenavir; Efavirenz (**§**IDV); Fluconazole; Grapefruit juice; Nevirapine (**§**IDV); Rifampicin and **§**Rifabutin (**§**IDV).
- Indinavir increases levels of Amprenavir; Clarithromycin; Ethinyl estradiol; Isoniazid; Ketoconazole; Nelfinavir; Nevirapine; **§**Rifabutin (**§**IDV); **§**Sildenafil; Trimethoprim and Zidovudine.
- Indinavir decreases levels of **§**Methadone (when IDV is given in combination with RTV).
- Potential interactions with anticonvulsants; other statins (Pravastatin can be used); oral contraceptives; tricyclic antidepressants; oral anticoagulants and Amiodarone.

Side Effects	Frequency	Severity
Nephrolithiasis or nephrotoxicity	+ +	+ + +
Abdominal pain	+ +	+ +
GI intolerance	+ +	+
Increase of indirect bilirubinaemia	+ +	+/-
Increase in liver function tests	+	+ +
Neutropenia	+	+ +
Rash	+	+/-
Taste perversion (metallic taste)	+	+/-
Headache	+	+/-
Asthenia	+	+/-
Dizziness	+	+/-
Thrombocytopenia	+	+/-
Alopecia/Hair loss	+	+/-
Hepatitis	-	+ +

Lopinavir/r (LPV/r)

Class

Protease Inhibitor (PI)

Available formulations

- Oral suspension: 80 mg/ml LPV + 20 mg/ml RTV
- Capsules: 133/33r mg (= 133.3 mg of Lopinavir + 33.3 mg Ritonavir in each cap.)

Storage

- Refrigerate
- Stable for two months at room temperature

Dose

Adults: 400/100r mg (3 caps.) twice daily **(WHO recommended)**

Children: 225 mg LPV/57.5 mg RTV per m^2 of body surface twice daily or the following table **(both WHO recommended)**

Weight	Dose
7-15 kg	12 mg/kg LPV + 3 mg/kg RTV
15-40 kg	10 mg/kg LPV + 5 mg/kg RTV
> 40 kg	400 mg LPV + 100 mg RTV (3 caps. or 5 ml)

LPV is combined with a fixed proportional dose of Ritonavir to increase its bioavailability.

If associated with Nevirapine or Efavirenz, dose should be increased: 4 caps. twice daily (adults) or 300 mg/75 mg per m^2 every 12 hours (children).

Food effect

Should be taken with food.

Half-life in plasma

From 5 to 6 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; inhibition of CYP3A4 and to a lesser extent of CYP 2D6 (Cytochrome P450 isoforms).
- If Didanosine or antiacids are administered, they should be taken at least one hour apart.
- Contraindicated drugs (LPV not to be taken with these drugs): Astemizole; Cisapride; Ergotamine and similar alkaloids; Flecainide; Garlic supplements; Lovastatin; Midazolam; Pimozide; Propafenone; Rifampicin; Simvastatin; St. John's wort *(hypericum perforatum)*; Terfenadine and Triazolam.
- Lopinavir levels are increased by Delavirdine and Ritonavir.
- Lopinavir levels are decreased by **§**Amprenavir (**§**LPV); Carbamazepine; Dexamethasone; Efavirenz (**§**LPV); Ketoconazole; Nevirapine (**§**LPV); Phenobarbital; Phenytoin; Rifampicin and Tenofovir.
- Lopinavir increases levels of Amiodarone, Amprenavir; **§**Atorvastatin; Bepridil; Calcium channel blockers; Clarithromycin; Ketoconazole; **§**Indinavir; Itraconazole; Lidocaine (systemic); Quinidine; **§**Rifabutin; **§**Saquinavir; Sildenafil and Tenofovir.
- Lopinavir decreases levels of **§**Amprenavir (**§**LPV); Atovaquone and **§**Methadone.
- Potential interactions with anticonvulsants; statins; oral contraceptives; tricyclic antidepressants; oral anticoagulants and immunosuppressants.
- Warning: oral solution contains 42.4% alcohol. Disulfiram-like reactions can occur with co-administration of Metronidazole, Cefamandole, Cefoperazone.

Side Effects	Frequency	Severity
Diarrhoea and loose stool	+ + +	+ +
Nausea	+ +	+
Abdominal pain	+	+
Vomiting	+	+/-
Rash	+	+/- (+ + in children)
Headache	+	+/-
Asthenia	+	+/-
Insomnia	+	+/-
Pain (not specified)	+	+/-
Elevated transaminase	+	+/-

Nelfinavir (NFV)

Class

Protease Inhibitor (PI)

Available formulations

- Oral powder: 50 mg/g
- Tablets: 250 mg

Storage

Room temperature

Dose

Adults: 1250 mg (5 tabs.) twice daily **(WHO recommended)** or 750 mg (3 tabs.) three times daily

Children: The table below indicates **WHO recommended** dosage or 30 mg/kg three times daily.

Age	Dose
< 1 yr	40-50 mg/kg three times daily or 65-75 mg/kg twice daily
>1 and <13 yrs	55-65 mg/kg twice daily
=13 yrs	Max. dose 1250 mg twice daily

Food effect

It should be taken with food; a light meal is usually sufficient.

Half-life in plasma

From 3.5 to 5 hours.

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; at CYP3A4 level (Cytochrome P450 3A4 isoform)
- If Didanosine or antiacids are administered, they should be taken at least one hour apart.
- Contraindicated drugs (NFV not to be taken with these drugs): Amiodarone; Astemizole; Cisapride; Ergotamine and similar alkaloids; Garlic supplements; Lovastatin; Midazolam; Quinidine; Rifampicin; St. John's wort *(hypericum perforatum)*; Simvastatin; Terfenadine and Triazolam.
- Nelfinavir levels are increased by Delavirdine; Efavirenz; Indinavir; Ketoconazole; Ritonavir and Saquinavir.
- Nelfinavir levels are decreased by Rifampicin and **§**Rifabutin (**§**NFV).
- Nelfinavir increases levels of Amprenavir; Indinavir; Lamivudine; **§**Rifabutin (**§**NFV); **§**Saquinavir and **§**Sildenafil.
- Nelfinavir decreases levels of Delavirdine; **§**Methadone and Zidovudine.
- Potential interactions with anticonvulsants; tricyclic antidepressants; immunosuppressants; oral contraceptives; statins and oral anticoagulants.

Side Effects	Frequency	Severity
Diarrhoea	+ + +	+
Rash	+	+/-
Nausea	+	+/-
Asthenia	+	+/-
Flatulence	+	+/-
Abdominal pain	+/-	+/-

Ritonavir (RTV)

Class

Protease Inhibitor (PI)

Available formulations

- Oral solution: 80 mg/ml
- Capsules: 100 mg

Storage

- Capsules should be refrigerated until dispensed; then, they are stable at room temperature for 30 days.
- Room temperature for oral solution (do not refrigerate)

Dose

Adults: **WHO** recommends to use Ritonavir only as booster for other PIs at low dosage

Possible dose if used alone: 600 mg (6 caps.) twice daily

Children: 400 mg/m2 of body surface every 12 hours

When used alone, to reduce adverse reactions/side effects, a patient should start treatment with 300 mg twice daily, then gradually increase the dose at 2-3 days intervals by 100 mg two times a day.

For children, start at 250 mg/m^2 every 12 hours, then gradually increase of 50 mg/m^2 per dose every 2-3 days.

Food effect

It can be taken with or without food; however, taking it with food may improve tolerability and bioavailability.

Half-life in plasma

From 3 to 5 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; very strong inhibition of CYP3A4 and of other CYP isoforms (Cytochrome P450 isoforms)
- If Didanosine or antiacids are administered, they should be taken at least two hours apart.
- Contraindicated drugs (RTV not to be taken with these drugs): Amiodarone; Astemizole; Atorvastatin; Bepridil; Cisapride; Clozapine; Ergotamine and similar alkaloids; Flecainide; Garlic supplements; Lovastatin; Midazolam; Pimozide; Propafenone; Quinidine; St. John's wort *(hypericum perforatum)*; Simvastatin; Terfenadine and Triazolam.
- Ritonavir formulations contain alcohol, which can produce Disulfiram-like reactions when co-administered with Disulfiram and other drugs that can

produce similar reactions, such as Metronidazole, Cefamandole and Cefoperazone.

- Ritonavir levels are increased by Clarithromycin; Delavirdine; Efavirenz; Fluconazole and Ketoconazole.
- Ritonavir levels are decreased by Nevirapine; Rifampicin and Tenofovir.
- Ritonavir increases levels of **§**Amprenavir (**§**RTV); Clarithromycin; **§**Desipramine; Efavirenz; **§**Indinavir (**§**RTV); Ketoconazole; Lopinavir; Nelfinavir; **§**Rifabutin; **§**Saquinavir (**§**RTV); **§**Sildenafil and Trimethoprim.
- Ritonavir decreases levels of Alprazolam; Atovaquone; Divaproex; Ethinyl estradiol; Lamotrigine; Meperidine; **§**Methadone; Phenytoin; Sulfamethoxazole; Theophylline (**§** may be required); Warfarin and Zidovudine.
- Potential interactions with analgesics; anticonvulsants; statins; oral contraceptives; tricyclic antidepressants; oral anticoagulants; immunosuppressants; Calcium channel blockers; sedative/hypnotics and Methamphetamine.

Attention: Oral solution contains 42% alcohol.

Side Effects	Frequency	Severity
Diarrhoea	+ + +	up to + + +
Nausea	+ + +	up to + + +
Vomiting	+ + +	+
Paresthesias (perioral or peripheral)	+ + (up to five weeks or longer)	+
Asthenia	+ +	+
Abdominal pain	+ +	+
Transaminase elevation	+ +	+
Taste perversion	+ +	+/-
Headache	+ +	+/-
Anorexia	+	+

Side Effects	Frequency	Severity
Elevated CPK	+	+/-
Elevated uric acid	+	+/-
Dizziness	+	+/-
Constipation	+	+/-
Flatulence	+	+/-
Bilirubinemia increase	+	+/-
Pancreatitis	+/-	+ + +
Allergic reactions	-	+ + +
Hepatitis	-	+ + +

Saquinavir (SQV)

Class

Protease Inhibitor (PI)

Available formulations

- Capsules: 200 mg (Hard Gelatin Capsules: Invirase®)
- Capsules: 200 mg (Soft Gelatin Capsules: Fortovase®)

Fortovase® soft gelatin capsules and Invirase® capsules are not bioequivalent and cannot be used interchangeably

Storage

- HGC: Room temperature
- SGC: Refrigerate; it can be kept at room temperature for up to 3 months

Dose

Adults (HGC and SGC): 1000 mg (5 caps.) SQV + 100 mg(1 caps.) RTV twice daily **(WHO recommended)**

Adults (HGC):	400 mg (2 caps.) twice daily + Ritonavir at 400 mg (4 caps.) twice daily (it is recommended only if administered with RTV)
Adults (SGC):	1200 mg (6 caps.) three times daily
Children:	Paediatric use not approved

Food effect

- HGC: No food effect if taken with Ritonavir; however, taking it with food may improve Ritonavir tolerability.
- SGC: It should be taken with a meal or up to two hours after a meal; no food effect if taken with Ritonavir.

Half-life in plasma

From 1 to 2 hours

Metabolism

Mainly in the liver

Interactions with other drugs

- Yes; inhibition of CYP3A4 (Cytochrome P450 3A4 isoform)
- Contraindicated drugs (SQV not to be taken with these drugs): Astemizole; Cisapride; Ergotamine and similar alkaloids; Garlic supplements; Indinavir (*in vitro* antagonism); Lovastatin; Midazolam; Rifabutin; Rifampicin; St. John's wort *(hypericum perforatum)*; Simvastatin; Terfenadine and Triazolam.
- Saquinavir levels are increased by Clarithromycin; Delavirdine (**§**SQV); Grapefruit juice; Ketoconazole; Lopinavir (**§**SQV); Nelfinavir (**§**SQV) and **§**Ritonavir (**§**SQV).
- Saquinavir levels are decreased by Amprenavir; Dexamethasone; Efavirenz; Nevirapine (should be given with SQV only if RTV is co-administered); Rifampicin (can be given with SQV only if RTV is co-administered) and Rifabutin (decrease dose if given with SQV+RTV).

- Saquinavir increases levels of Clarithromycin; Nelfinavir; §Sildenafil and Terfenadine.
- Saquinavir decreases levels of Amprenavir and Efavirenz.
- Potential interactions with and anticonvulsants; statins; Methadone; oral contraceptives; tricyclic antidepressants and oral anticoagulants.

Side Effects	Frequency	Severity
GI intolerance	+ + +	+
Headache	+ +	+/-
Elevated transaminase	+	+/-
Fatigue	+	+/-
Rash	+	+/-
Thrombocytopaenia	+	+/-

Class Adverse Drug Reactions to Protease Inhibitors (PIs)

Hyperglycemia

New onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of existing diabetes mellitus, as well as hyperglycemia, insulin resistance or glucose tolerance have all been reported in patients receiving protease inhibitors. Insulin resistance occurs in up to 40% of patients treated with PIs, while hyperglycemia has been reported in 3-17% of patients receiving PIs (median onset is 60 days after initiation of therapy, ranging from 2-390 days); about 1% of these patients develop clinical evidence of diabetes.

The reversibility of these events is currently unknown, due to limited data and still limited follow up of patients. Some patients were able to continue the PI therapy and initiated treatment with oral hypoglycemic agents or insulin.

An option for early diagnosis is to perform routine fasting blood glucose measurements at regular intervals during treatment. Asking the patient to report immediately the occurrence of suspect signs and symptoms as polydipsia, polyphagia or polyuria can also be useful.

HIV-infected patients with pre-existing diabetes should be closely monitored when PIs are prescribed.

Fat redistribution

Modifications in body fat distribution - sometimes referred to as "lipodystrophy syndrome", "fat redistribution syndrome", or "pseudo-Cushing's syndrome" - are frequently (13-84%) observed in patients treated with protease inhibitors. These changes have also been described with NRTI therapy (particularly with d4T-containing regimens).

The most typical clinical findings include central obesity and peripheral fat wasting. The observed changes include visceral fat accumulation, dorsocervical fat accumulation (known as "buffalo hump"), extremity wasting with venous prominence, loss of buttock fat, facial thinning, breast enlargement, and lipomatosis. Sometimes, patients may have a cushingoid appearance despite the absence of measurable abnormalities in adrenal function.

The pathogenetic mechanism of these manifestations is still unclear. Actually, similar findings have also been reported in HIV-infected patients not receiving protease inhibitors, although with a lower frequency.

Although not definitively established, central fat accumulation appears to be more associated with PIs and peripheral fat wasting with NRTIs. Hyperlipidemia and insulin resistance are frequently but not always associated with lipodystrophy. Therapeutic strategies have included switching classes of antiretroviral drugs and exercise training. Reversal of body shape changes may not occur or may occur only slowly once the offending antiretroviral agent(s) has (have) been discontinued. Specific drug treatments for this condition are being actively investigated.

Hyperlipidemia

Changes in triglycerides and/or cholesterol blood levels have been observed very frequently, even in the absence of fat redistribution. Although all PIs have been implicated, Ritonavir produces substantial increases in triglycerides and cholesterol most frequently and reaching higher blood levels.

The observed prolonged important increases in triglycerides and/or cholesterol are of concern because of the possible association with cardiovascular events and pancreatitis. Actually, premature coronary artery disease, cerebrovascular disease, and cholelithiasis in patients receiving PI therapy have been reported.

Monitoring serum triglycerides and cholesterol at regular intervals during treatment can be an option for assessment of cardiovascular risk. However, a complete evaluation of all other independent cardiovascular risk factors (e.g. smoking, diet, weight, etc.) is necessary, and it should be suggested to patients to reduce them as much as possible.

Intervention is usually recommended for triglycerides levels >750-1,000 mg/dl and/or LDL cholesterol levels >130 mg/dl (in individuals without known coronary disease and with two or more coronary risk factors) or >160 mg/dl (in individuals without known coronary disease and with fewer than two coronary risk factors). However, the effectiveness of dietary modifications and lipid lowering drugs is not yet clear. In some cases, discontinuation of PIs showed to be beneficial; but such a decision requires a careful risk-benefit analysis.

Increased bleeding episodes in patients with haemophilia

An increased number of spontaneous bleeding episodes has been observed in patients with hemophilia A and B, and treated with PIs. The median time to onset of bleeding episodes was 22 days after initiation of PI therapy. Most of the reported episodes involved joints and soft tissues; however, more serious bleeding episodes as intracranial and gastrointestinal bleeding have been reported, too.

There are patients who require additional coagulation factor while continuing PI treatment.

Avascular necrosis

Avascular necrosis (AVN) is considered another possible complication of HAART. However, many patients with AVN present other characteristic risk factors for it, as alcohol abuse, hyperlipidemia, corticosteroid use and/or hypercoagulability. The most common sites are the femoral or the humeral head. Reported rates are between 0.3 and 1.3% of patients treated with potent ART.

Osteopenia/osteoporosis

Osteopenia/osteoporosis have been increasingly reported in adults and children receiving PI-containing HAART. The association of these findings with potent ART has

not been definitively established, although the risk appears higher in patients receiving PI than non-PI-containing regimens.

However, a recent study showed that men receiving protease inhibitors had a higher incidence of osteopenia and osteoporosis according to WHO definitions. Subjects receiving protease inhibitors had greater central/appendicular adipose tissue ratios than patients not receiving PIs. Furthermore, osteopenia and osteoporosis are unique metabolic complications that appear to be independent of adipose tissue maldistribution.

USEFUL INTERNET LINKS

- http://www.who.int/HIV_AIDS/HIV_AIDS_Care/Scaling_Up_ARV_Guidelines_Final_E.pdf
- http://www.who.int/HIV_AIDS/HIV_AIDS_Care/ARV_Draft_April_2002.pdf
- http://www.who.int/medicines/organization/qsm/activities/pilotproc/pilotproc.shtml
- http://www.who.int/medicines/organization/par/edl/expertcomm.shtml
- http://www.medscape.com/Home/Topics/AIDS/AIDS.html
- http://www.amfar.org
- http://www.hivandhepatitis.com
- http://www.bnf.org/AboutBNFFrameHowtoUse.htm
- http://www.cdc.gov/hiv/treatment.htm
- http://www.ama-assn.org/special/hiv/hivhome.htm
- http://www.fda.gov/oashi/aids/hiv.html
- http://www.hivatis.org
- http://www.hopkins-aids.edu/
- http://www.aidsmeds.com/
- http://www.aidsmap.com
- http://aids.org
- http://www.thebody.com/
- http://www.hivnat.org/
- http://hivinsite.ucsf.edu/InSite
- http://www.paho.org/English/HCP/HCA/antiretrovirals_HP.htm

There are several drug companies manufacturing antiretroviral drugs, which maintain websites. The exact addresses may be located using search engines.

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(11) *Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study*. J Fellay et al. Lancet 2001; 358: 1322-1327.

(12) *The Medical Letter* – It frequently publishes updates on different aspects of antiretroviral drugs.

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