

# ANTIRETROVIRALS FOR HIV : A COMPILATION OF FACTS AND PRODUCT INFORMATION





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# **Antiretrovirals for HIV: a compilation of facts and product information**

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# A

## BBREVIATIONS AND ACRONYMS

3TC	lamivudine
ABC	abacavir
ALT	alanine transaminase
APV	amprenavir
ART	antiretroviral therapy
AST	aspartate aminotransferase
ARV	antiretroviral (drug)
ATZ	atazanavir
AUC	area under the curve
AZT	azidothymidine (equivalent to zidovudine)
CD4	CD4+ T-lymphocyte
CNS	central nervous system
CPK	creatine phosphokinase
CT	computed tomography
CYP	cytochrome P450
d4T	stavudine
ddI	didanosine
DHHS	Department of Health and Human Services of USA
DNA	deoxyribonucleic acid
EC	enteric coated
EFV	efavirenz
FDA	Food and Drug Administration
FDC	fixed-dose combination
Fos-APV	fosamprenavir
FTC	emtricitabine
GI	gastrointestinal
HGC	hard-gelatine capsules
HIV	human immunodeficiency virus
IDV	indinavir
INR	international normalized ratio
IRIS	immune reconstitution inflammatory syndrome
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LPV	lopinavir

LPV/r	lopinavir/ritonavir
MTCT	mother-to-child transmission
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NsRTI	nucleoside reverse transcriptase inhibitor
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PI	protease inhibitor
PCP	<i>Pneumocystis jiroveci</i> (previously <i>Pneumocystis carinii</i> ) pneumonia
PEPFAR	US President's Emergency Plan for AIDS Relief
PMTCT	prevention of mother-to-child transmission
r	ritonavir (when given in association with other PIs for boosting effect)
RNA	ribonucleic acid
RTV	ritonavir
SGC	soft-gelatine capsules
SJS	Stevens-Johnson syndrome
SQV	saquinavir
TB	tuberculosis
T-20	enfuvirtide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TMP/SMX	trimethoprim/sulfamethoxazole
UK	United Kingdom
ULN	upper limit of normal
UNICEF	United Nations Children's Fund
US	United States
WHO	World Health Organization
ZDV	zidovudine



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# P REFACE

The World Health Organization (WHO) assists countries in the planning and implementation of comprehensive HIV prevention, care and treatment programmes. This role assumed a greater urgency with the WHO commitment to scale up antiretroviral therapy (ART) to reach three million people living with HIV/AIDS (PLHA) by the end of 2005 (the “3X5 Initiative”). To maintain momentum and build upon the progress made, in July 2005 leaders of the G8 group of industrialized countries announced their intention to work with WHO, UNAIDS and other international bodies to develop and implement a package for HIV prevention, treatment and care, with the aim of as close as possible to universal access to treatment for all those who need it by 2010. This goal was subsequently endorsed by all UN Member States at the High Level Plenary Meeting of the 60th Session of the UN General Assembly in September 2005. The scope of universal access in the health sector has been defined as follows:

- Universal access refers to access to prevention, treatment, care and support interventions for all who need it.
- Access (availability, affordability and acceptability) should be measured at the country level within the context of globally accepted guiding principles, ensuring access for all in need to services that provide a minimal standard of quality.
- Coverage indicates the optimal availability and utilization, in accordance with the epidemiology, of a specific intervention.

With worldwide drug price reductions, ART is accessible to more PLHA. Effective implementation of antiretroviral treatment programmes requires more than the provision of drugs. Training and capacity-building of health-care workers is essential if these complex and still expensive medicines are to be used effectively and sustainably.

This compilation of facts and product information forms part of a set of materials available to health-care workers caring for PLHA. They are intended to be a technical resource and reference for physicians, pharmacists and nurses managing patients on ART.

# 1

## INTRODUCTION

### Features

This document is a compilation of current facts and product information about antiretroviral (ARV) drugs that are commonly used in resource-constrained settings. The sections about individual drugs include information about the class of the drug, available formulations, storage, dosage, known interactions with other drugs (including other ARVs) and main side-effects.

All the details provided here come from labelling information, data published in WHO documents, international scientific literature, reports presented at international conferences, information from medicines regulatory authorities and national guidelines for antiretroviral treatment (ART) of different countries, and from websites dedicated to the treatment of HIV infection.

### Effective use of this document

This compilation is meant to be a supplementary source of information for physicians and does not replace the manufacturer's product information sheet or existing current national guidelines for ART of any country. The information listed here is updated as of July 2006.

The process of choosing an ARV regimen is a complicated one and many aspects need to be considered. The new treatment regimens recommended by WHO can be found in the section on "Choice of antiretroviral drugs".

This document is not intended to be a guideline on treatment, and the reader should consult national or regional treatment guidelines before prescribing ART. In addition to country publications, the following guidelines have been developed:

- *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual.* New Delhi, World Health Organization Regional Office for South-East Asia, 2006.
- *Management of HIV infection and antiretroviral therapy in infants and children: a clinical manual.* New Delhi, World Health Organization Regional Office for South-East Asia and United Nations Children's Fund, 2006.

- *Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access.* Geneva, World Health Organization, 2006.
- *Antiretroviral therapy for HIV infection in infants and children in resource-limited settings: towards universal access.* Geneva, World Health Organization, 2006.
- *WHO HIV prevention and treatment guidelines.* Geneva, World Health Organization, 2006.
- *Prequalification programme: access to HIV drugs and diagnostics of acceptable quality.* Geneva, World Health Organization. Available at [http://mednet3.who.int/prequal/lists/hiv\\_suppliers.pdf](http://mednet3.who.int/prequal/lists/hiv_suppliers.pdf)
- *Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS.* Geneva, World Health Organization, 2005.
- *WHO model formulary.* Geneva, World Health Organization, 2004.

# 2

## MODE OF ACTION OF ANTIRETROVIRAL DRUGS

Different types of ARVs act in different ways to prevent the replication of HIV in the human body. These different pathways are briefly described below.

### Nucleoside reverse transcriptase inhibitors (NsRTIs) and Nucleotide reverse transcriptase inhibitors (NtRTIs).

NtRTIs and NsRTIs act by incorporation into the DNA of the virus (competing with natural nucleotides/nucleosides), 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 (NNRTIs)

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

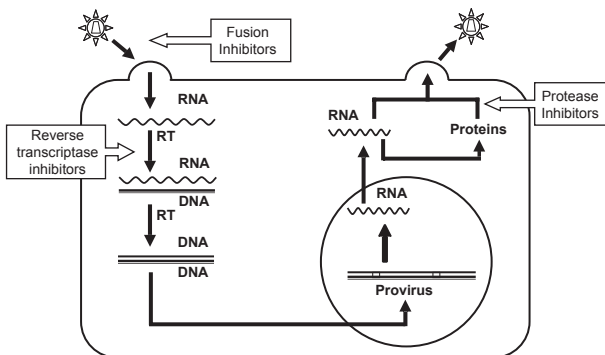
### Protease inhibitors (PIs)

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

### Fusion inhibitors

Fusion inhibitors (peptides) act by binding to a region of the gp41 transmembrane glycoprotein of HIV and prevent virus–cell fusion.

**Figure 1. Mode of action of different types of ARVs**



# 3

## CHOICE OF ANTIRETROVIRAL DRUGS

The choice of regimen depends on a number of factors. These include efficacy, tolerability, cost, availability, likelihood of adherence, availability of fixed-dose combinations (FDCs, such as d4T-3TC-NVP, AZT-3TC-NVP and AZT-3TC-ABC, in one tablet), drug interactions, potential for alternative treatment options in the event that the initial drug regimen fails and lack of requirement for a cold chain (refrigeration). With the exception of prevention of mother-to-child transmission (PMTCT) of HIV, single and dual ART should never be used. Newer FDCs are constantly being developed, with FTC-TFV and once daily FTC-TFV-EFV being recently approved by the FDA.

The most recent WHO recommendations for treatment regimens are reflected in the following publications:

- *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual.* New Delhi, World Health Organization Regional Office for South-East Asia, 2006.
- *Management of HIV infection and antiretroviral therapy in infants and children: a clinical manual.* New Delhi, World Health Organization Regional Office for South-East Asia and United Nations Children's Fund, 2006.
- *HIV/AIDS treatment and care for injecting drug users in Asia: a guide to essential practice.* World Health Organization Regional Office for South-East Asia and Regional Office for the Western Pacific, draft 2006.
- *Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access.* Geneva, World Health Organization, 2006.
- *Antiretroviral therapy for HIV infection in infants and children in resource-limited settings: towards universal access.* Geneva, World Health Organization, 2006.
- *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: towards universal access. Recommendations for a public health approach.* Geneva, World Health Organization, 2006.

# 4

## HARMFUL INTERACTIONS BETWEEN ANTIRETOVIRAL DRUGS

The following combinations of ARVs **should not be prescribed together**, because of antagonism, toxicity or poor efficacy.

- Tenofovir (TDF) should not be combined with abacavir (ABC).
- Zidovudine (AZT) should not be combined with stavudine (d4T).
- Saquinavir (SQV) should not be combined with indinavir (IDV).
- Stavudine (d4T) should not be combined with didanosine (ddI).
- Zalcitabine (ddC) is not recommended due to reduced efficacy and more toxicity compared with other NsRTIs.
- Didanosine (ddI) and tenofovir (TFV) should preferably not be co-administered.

WHO recommends that, among PIs, nelfinavir (NFV) should be used as single PI only if ritonavir (RTV) is not available, while IDV, lopinavir (LPV) and SQV should be used in association with low doses of RTV. Unboosted atazanavir (ATZ) can be used for treatment-naive patients. However, RTV-boosted treatment should be used for treatment-experienced patients.

The use of RTV to increase plasma concentrations of other PIs (booster effect) has rapidly evolved from an investigational concept to widespread practice. RTV increases plasma concentrations of other PIs by at least two mechanisms— inhibition of gastrointestinal cytochrome P450 (CYP450) during absorption, and metabolic inhibition of hepatic CYP450.

Unboosted doses of individual PIs may result in trough drug levels that are below the effective antiviral concentration; this may offer an opportunity for viral replication. In contrast, protease “boosting” or “enhancement” by RTV increases the trough levels of other PIs well above the  $IC_{50}$  or  $IC_{95}$ , minimizing opportunities for viral replication, and potentially allowing for drug activity even against some resistant strains of HIV. In addition, these PIs/r may lead to more convenient regimens in terms of pill burden, scheduling and elimination/ reduction of food restrictions.



# 5

## 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 rise daily to about  $3 \times 10^{-3}$  spontaneous changes (mutations) in its genetic sequence. The ultimate size of a viral population containing a mutation is 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. The ongoing production of genetic variants of HIV results in a continuous selection for the “fittest” virus population. The main reasons for mutation (resistance) development are poor adherence to treatment, reduced drug absorption, infection with drug-resistant HIV and subtherapeutic dosing.

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

ART 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 within the available classes of ARV 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 lamivudine (3TC) and emtricitabine (FTC), especially if they are used as part of a regimen that produces incomplete suppression of viral replication.

A few drugs, namely efavirenz (EFV), 3TC and nevirapine (NVP), present a very low “genetic barrier” to resistance because a single mutation is sufficient to produce resistance.

# 6

## REASONS FOR AND INTERPRETATION OF DRUG INTERACTIONS

This document provides an overview of current knowledge of ARV drug interactions. In particular, PIs and NNRTIs have complex metabolism and interactions and, when given in combination, they often affect each other's drug levels and potency. The knowledge of these combinations and interactions is continuously evolving. Close monitoring is advised when using combinations of PIs or PIs with NNRTIs. Treating physicians are strongly advised to verify all information with an HIV/AIDS specialist, an expert pharmacist or the manufacturer's prescribing information leaflet and product insert.

Many ARV drugs, in particular the NNRTI and PI classes, are metabolized in the liver and they can both inhibit or induce the CYP450 system. This results in interactions with other ARV drugs as well as other drugs that can be taken concurrently. If a dose modification in one or both the interacting drugs is recommended, a note (§ = dose modification recommended) is inserted in the text. Specific recommendations are given where these are available. As this is a continually evolving field of research, the reader should refer to the most recent available indications or selected websites. In case of interaction with methadone, no specific dose adjustment can be specified; the dose of methadone should be adjusted in case of opioid withdrawal and increased till withdrawal symptoms disappear. The table in chapter 12 provides further information on the interactions of ARVs with methadone and actions to be taken, if any.

In addition to dose modifications, some combinations of drugs are contraindicated because of the potential for serious and life-threatening interactions.

# 7

## DOSAGE

- In case of renal impairment the dosage of ARV drugs may need to be modified. In some cases, a clear relationship between creatinine clearance and the new dosage has been established. For details, the reader is referred to the manufacturer's prescribing information.
- The dosage recommended by WHO of some PIs is different from the registered dose recommended by the manufacturer. The choice of the WHO-recommended dosage is based on expert opinion as contained in the following documents:  
*Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access*, Geneva, World Health Organization, 2006; and  
*Antiretroviral therapy for HIV infection in infants and children in resource-limited settings: towards universal access*, Geneva, World Health Organization, 2006.
- Dosing in children is usually based on either weight or body surface area. As these change with growth, drug doses must be adjusted to avoid the risk of underdosage. Standardization is important and it is desirable to provide health-care workers with a table of simplified drug doses that can be administered according to weight bands. Such tables may vary between localities in accordance with the availability of ARV drugs and formulations in the concerned country. WHO has developed prototype dosing tables and tools<sup>1</sup> to assist countries with standardization and calculation of drug doses (*Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach*. Geneva, WHO, 2006). Fixed-dose tablet combinations and/or oral solutions should be chosen if available, depending of the age of the child.

For calculating dosages for children, the body surface area (BSA) is often used. Body surface area can be calculated with the following equation:

$$\text{BSA (m}^2\text{)} = \sqrt{(\text{height [cm]} \times \text{weight [kg]})/3600}$$

However, for ARVs, dosing on the basis of weight is recommended.

---

<sup>1</sup> A web-based tool to assist with calculating dosages and dosing tables is being developed.

# 8

## INTERPRETATION OF DRUG-RELATED SIDE-EFFECTS

The causes of any new symptoms or signs developing after the initiation of ART should be identified whenever possible. New symptoms may be related to intercurrent illness or due to the adverse effects of ARV drugs. Shortly after commencing treatment, certain opportunistic infections or other inflammatory conditions may become clinically apparent as part of the immune reconstitution inflammatory syndrome (IRIS).

If new complaints are due to the 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.

Adverse effects of ARV drugs can be detected by targeted history-taking, and physical and laboratory examination. In this way, adverse effects such as anaemia and neutropenia, pancreatitis, hepatitis, nephrolithiasis and serious hypersensitivity reactions can be detected early and remedial action taken.

For better adherence to treatment, patients should be told of the possible occurrence of side-effects before starting ARV drugs. This patient education will reinforce the acceptability of minor and/or transient side-effects.

The drug-related side-effects mentioned in this compilation have been chosen because of their clinical relevance, frequency of reporting, severity and high correlation with the drug.

# 9

## WRITING A PRESCRIPTION

A prescription is an instruction from a prescriber to a dispenser. The prescriber is not always a doctor but can also be a paramedical worker, such as a medical assistant, a midwife or a nurse. The dispenser is not always a pharmacist, but can be a pharmacy technician, an assistant or a nurse. Every country has its own standards for the minimum information required for a prescription, and its own laws and regulations to define which drugs require a prescription and who is entitled to write it. There is no global standard for prescriptions and every country has its own regulations. The most important requirement is that the prescription be clear. It should be legible and indicate precisely what should be given in a language that the dispenser can understand<sup>2</sup>.

### Name and address of the prescriber, with telephone number (if possible)

This is usually pre-printed on the form. If the pharmacist/dispenser has any questions about the prescription they should try to contact the prescriber if possible.

### Date of the prescription

### Name and strength of the drug

R/(not Rx) is derived from *recipe* (Latin for “take”). After R/you should write the name of the drug and the strength. It is strongly recommended to use the generic (nonproprietary) name<sup>3</sup>. This facilitates education and information. It means that you do not express an opinion about a particular brand of the drug, which may be unnecessarily expensive for the patient. It also enables the pharmacist/dispenser to maintain a more limited stock of drugs, or dispense the cheapest drug. However, if there is a particular reason to prescribe a special brand, the trade name can be added. Some countries allow generic substitution by the pharmacist and require the addition “*Do not substitute*” or “*Dispense as written*” if that brand, and no other, is to be dispensed.

The strength of the drug indicates how many milligrams of the drug each tablet, suppository, or millilitre of fluid should contain. Internationally accepted abbreviations should be used: g for gram, ml for millilitre. Try to avoid decimals

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<sup>2</sup> See also: *Guide to good prescribing. A practical manual*. Geneva, World Health Organization, 1994 (WHO/DAP/94.11).

<sup>3</sup> It is assumed that only medicines of assured quality are available in the supply system.

and, where necessary, write words in full to avoid misunderstanding. For example, write levothyroxin 50 micrograms, not 0.050 milligrams or 50  $\mu\text{g}$ . Badly handwritten prescriptions can lead to mistakes, and it is the legal duty of the doctor to write legibly. In prescriptions for controlled drugs or those with a potential for abuse it is safer to write the strength and total amount in words to prevent tampering. Instructions for use must be clear and the maximum daily dose mentioned. Use indelible ink.

### **Dosage form and total amount**

Use only standard abbreviations that will be known to the pharmacist/dispenser.

### **Information for the package label**

S stands for *signa* (Latin for “write”). All relevant information following the S or the word “label” should be copied by the pharmacist/dispenser onto the label of the package. This includes how much of the drug is to be taken, how often, and any specific instructions and warnings. These should be given in the local language. Do not use abbreviations or statements like “as before” or “as directed”. When stating “as required”, the maximum dose and minimum dose interval should be indicated. Certain instructions for the pharmacist/dispenser, such as “Add 5 ml measuring spoon” are written here, but of course are not copied onto the label.

### **Prescriber’s initials or signature**

### **Name of the patient; age and weight (for children and the elderly)**

### **Examples of prescriptions**

Dr W. WHO  
11, WHO street  
WHO Town  
Tel: 123456

Date:

R/

Abacavir 300 mg tablet — 60 tablets, 1 tablet 2 times per day with or without food;

xx

Tenofovir 300 mg tablet — 30 tablets, 1 tablet daily taken with food;

xx

Lamivudine 150 mg — 60 tablets, 2 tablets daily, with or without food;

xx

Efavirenz 600 mg tablet — 30 tablets, 1 tablet per day, with or without food.

Mr: A. Smith  
Address:  
Age: 35 years

Dr W. WHO  
11, WHO street  
WHO Town  
Tel: 123456

Date:

R/

Lamivudine (150 mg)/Zidovudine (300 mg)/Abacavir (300 mg) tablet — 60 tablets;

2 tablets per day with or without food;

xx

Nevirapine 200 mg tablets — 60 tablets, 2 tablets 2 times per day.

Mr: A. Smith  
Address:  
Age: 35 years

Dr W. WHO  
11, WHO street  
WHO Town  
Tel: 123456

Date:

R/

Zidovudine 10 mg/ml solution — 240 ml, 9 ml 3 times per day with or without food.

xx

Lamivudine 10 mg/ml solution — 240 ml, 6 ml 2 times per day with or without food.

xx

Nevirapine 10 mg/ml solution — 240 ml, 6 ml 1 time per day for two weeks, then 10.5 ml 2 times per day

1 disposable syringe for dispensing the dosages.

Ms: B. Smith  
Address:  
Age: 5 years  
Weight/height: 15 kg/100 cm

# 10

## ADHERENCE TO ANTIRETROVIRAL THERAPY

Studies of drug adherence in the developed world have demonstrated that higher levels of drug adherence are associated with improved virological, immunological and clinical outcomes, and that adherence rates  $>95\%$  are necessary to maximize the benefits of ART. It is a challenge to achieve rates this high over a long period of time. Numerous approaches to improving adherence have been investigated in the developed world and have begun to be explored in resource-limited settings. Particularly in the absence of HIV-RNA (viral load) testing to detect early ART failure, adherence is even more crucial to delay or avoid the development of drug resistance and ensure maximum durability of the first-line ARV regimen.

A key to any successful adherence strategy is the education of patients before the initiation of ART to assess their understanding of ART and their treatment readiness. Adherence counselling includes basic information about HIV and its manifestations, the benefits and side-effects of ARV medications, how the medications should be taken and the importance of not missing any doses. Peer counsellors and visual materials can be particularly helpful in this process. The provision of ART as part of a continuum of care for PLHA is a way to ensure ongoing care and adherence. The model of day-care centres in northern Thailand could be applied, where comprehensive care includes a range of services offered to PLHA.

Keys to successful adherence once treatment has begun include trying to minimize the number of pills (in part through the use of FDCs), the packaging of pills (co-blister packs when available), the frequency of dosing (no more than twice-daily regimens), avoidance of food restrictions, fitting the intake of ARVs into the patient's lifestyle, and involving relatives, friends and/or community members in support of the patient's adherence.

Adherence in women during the postpartum period may be particularly problematic and require special support for the woman, as the stresses of caring for a newborn may lead the woman to pay less attention to her own health care.

Adherence in children is a special challenge, particularly if the family unit is disrupted by health, economic or political conditions. Family-based HIV care programmes are some of the best approaches to assure childhood health. Also, it is imperative that paediatric formulations be improved and made widely available. These need to match the adult regimens, where possible, to ensure that family-based care can be pursued effectively.



# 11

## RELIABLE SUPPLY OF ANTIRETROVIRAL DRUGS

ARV treatment is lifelong and must be uninterrupted. Thus, a crucial factor is a reliable system for the supply of ARV drugs of assured quality, efficacy and safety, available in sufficient quantities where and when they are needed, which are affordable for the community and individual patients.

### Antiretroviral drugs supply management

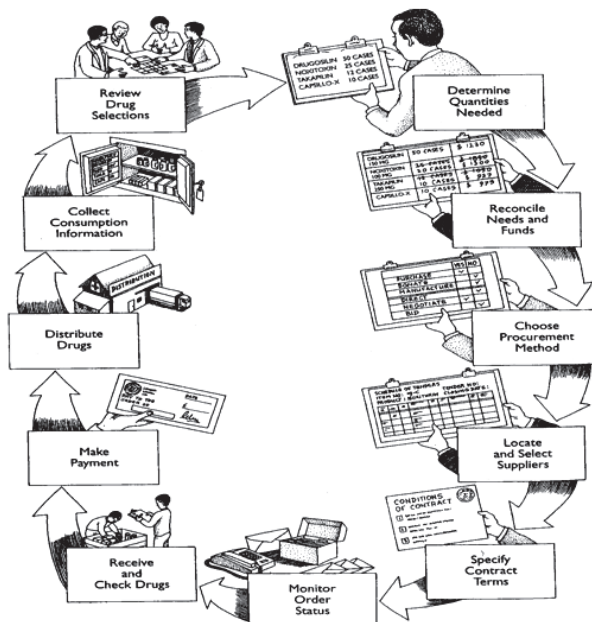
ARV drugs supply management is quite different and particularly challenging compared with traditional drug supply management:

- ARV therapy is lifelong and requires an uninterrupted supply of relatively expensive drugs.
- There may be a rapid increase in the number and distribution of patients under treatment, which is a challenge to forecasting the need for these drugs. Despite this need, funding for procuring ARV drugs is limited.
- Stock-outs will lead to insufficient adherence, treatment failure and development of resistance.
- Patients need frequent monitoring and alternative treatment regimens may have to be used soon after initiation of treatment.
- The supply system needs to be flexible due to drop-outs, failure of treatment, transfer-in (-out) and deaths.
- ARV therapy requires clinical and laboratory monitoring; an uninterrupted supply of diagnostic equipment, kits and reagents is therefore needed.
- In addition to ARV drugs, there must be a reliable supply of drugs for the treatment of opportunistic infections.
- Regulatory issues need to be considered such as registration and patent status.
- Some ARV drugs have at times been in short supply globally.

The above factors indicate why there may be a need for a special national mechanism or organization for ARV supply management. This is especially so where existing public sector supply systems are already severely stressed and cannot cope with the additional burden.

ARV supply management is about forecasting needs. It is a complex, cyclical process that can be illustrated as follows:

**Figure 2. The supply management cycle<sup>4</sup>**



The following are the most important steps in the cycle:

### Selection of ARVs to use

The first step is to decide upon which ARVs to use based on national standard treatment guidelines. If such guidelines do not yet exist, it may be helpful to consider the WHO model treatment guidelines (*see* chapter 3).

### Selection of products

Having decided on which ARVs to use, one has to identify the manufacturers/suppliers who can deliver products of adequate quality and at the most affordable prices. Most countries require by law that medicines to be placed on the market need a marketing authorization or registration based on scientific evidence that the products fulfil international or national standards related to safety, efficacy and quality (*see* “Product registration”). In countries without such systems in place,

<sup>4</sup> Reproduced with permission from: Management Sciences for Health and World Health Organization. *Managing drug supply*, 2nd edition. West Hartford, CT, Kumarian Press, 1997.

one can select products that have been approved by the WHO prequalification programme for ARVs (see “WHO prequalified antiretroviral drugs”).

Donors normally require that medicines bought using their funds should be registered in the country of manufacture and in the importing country. Some have further requirements such as registration in countries with stringent regulatory authorities (see “Product registration”). Others require that the medicines be WHO prequalified. The US President’s Emergency Plan for AIDS Relief (PEPFAR) requires that ARVs bought with its funds are approved by the US Food and Drug Administration (FDA).

## Product registration

It is essential to ensure that ARVs selected for use are safe, efficacious and of assured quality. In countries with well developed regulatory systems for medicines, this is taken care of through the process of registration (marketing authorization). Through this process the manufacturers provide scientific evidence that their products fulfil international or national standards related to safety, efficacy and quality. The process of evaluating the evidence is a lengthy one and requires sufficient human resources with the capability of assessing scientific documents. In addition, laboratory testing may be required.

Countries that do not have a well developed medicines regulatory system could rely on registration of ARVs in other countries. The Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) has adapted this approach in its procurement policy (*Guide to the Global Fund’s policies on procurement and supply management*. The Global Fund to fight AIDS, Tuberculosis and Malaria, 2005. Available at <http://www.theglobalfund.org/en/about/procurement/policies>) through defining countries with regulatory authorities that are considered stringent<sup>5</sup> and by relying on their assessment.

Medicines registered in these countries do not need a thorough evaluation as this has already been carried out. Thus, the process of registration can be made shorter, making the medicines available without delays. Fast-track or provisional registration is a mechanism that can be introduced by national regulatory authorities to make ARV medicines available quickly.

## WHO prequalified antiretroviral drugs

Many international, regional and national organizations are involved in the procurement of medicines. The supply of effective medicines of acceptable quality

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<sup>5</sup> Pharmaceutical Inspection Convention Scheme (PIC/s) participating countries: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Malaysia, Netherlands, Norway, Portugal, Romania, Singapore, Slovak Republic, Spain, Sweden, Switzerland, United Kingdom.

for the treatment of HIV/AIDS, malaria and TB has become a major concern at both the international and the country levels. The WHO prequalification programme aims to facilitate access to medicines of acceptable quality by assessing their compliance with WHO-recommended standards. The programme was initiated by WHO in collaboration with UNAIDS, UNDP, UNFPA and UNICEF.

Two procedures are used to assess the acceptability of medicines:

1. Evaluation of product data and information provided by manufacturers and suppliers; and
2. Inspection of manufacturing sites to ensure that good manufacturing practices (GMP) are in place.

Manufacturers who wish to prequalify their products may express their interest to WHO. After ensuring that the submitted documentation related to products and manufacturing facilities is satisfactory, WHO may organize a detailed evaluation of product dossiers and inspection of the manufacturing site. Only products and manufacturing sites that are found to meet the recommendations in the WHO guidelines are published in a list of suppliers. The list is intended to be a tool to guide the selection of suppliers for procurement purposes.

Countries are recommended to use these lists when sourcing products for procurement to ensure that medicines of acceptable quality are purchased. This will also facilitate the registration of medicinal products, as the listed products and suppliers already comply with WHO guidelines for registration and GMP.

The lists of the most recent WHO prequalified ARVs and additional information about the WHO prequalification programme can be found at: [http://mednet3.who.int/prequal/lists/hiv\\_suppliers.pdf](http://mednet3.who.int/prequal/lists/hiv_suppliers.pdf)

In addition to the above, the patent status of the products that one wishes to import must be considered to avoid potential violation of intellectual property rights.

### Forecasting of ARV needs

Having selected the medicines to use as well as identified the sources (manufacturers/suppliers), the next step is to estimate how much of each medicine to order. Forecasting the need for medicines is usually based on past consumption of the medicines in question, because this method is relatively easy. However, ideally, forecasting should be based on the number of patients to be treated as well as how they will be treated. Thus, while calculating the need for ARV drugs, one has to consider the number of patients together with the standard treatment guidelines. In addition, HIV/AIDS treatment is being scaled up, meaning that in addition to the number of patients already on treatment, treatment programmes enrol more patients every month; thus, the number of patients may increase rapidly from month to month. When a patient starts on a treatment regimen, because of adverse

reactions and toxicity, the regimen may have to be changed. This makes forecasting complicated<sup>6</sup>. Some organizations (The Clinton Foundation, PEPFAR) have developed methods by which needs can be calculated based on certain assumptions such as number of patients on various regimens and number of new patients to be enrolled. HIV/AIDS treatment programmes must have systems in place to monitor how patients react to the treatment. Such systems should be linked to the forecasting system so that changes noticed via the monitoring system can be used to forecast more accurately the types and quantities of medicines likely to be needed.

## Procurement

Procurement is aimed at purchasing the right products of adequate quality at the right time in the quantities needed at an affordable price. The previous section described how to select medicines and products, and how to estimate the quantities to be procured. The next step is to identify the suppliers, place the orders and decide upon the contracts to be used with the suppliers. In countries with a registration system in place, one can only procure products that are already registered, meaning that, to a large extent, the suppliers are already fixed. In most countries, public procurement systems are based on tenders, in which quotations are called for to cover an annual or bi-annual need. One benefit of such long tender periods is that one can take advantage of the economies of scale. Generally, the bigger the quantity ordered, the better the price offered. To select the right product at a reasonable price depends on the availability of price information. Experience shows that resource-limited countries at times pay higher prices than developed countries. To be able to negotiate reasonable prices, price information is crucial. Information on the prices of medicines can be found at <http://www.who.int/medicines/areas/access/ecofin/en/index.html>.

However, for ARV drugs, such systems may not be flexible enough as frequent adjustment of the supply may be needed due to change of regimens and even change of treatment guidelines. A more flexible system should be established, which is not easy as public procurement in most countries is regulated by law.

For further reading, refer to: *Operational principles for good pharmaceutical procurement* (Geneva, WHO, 1999) and *Practical guidelines on pharmaceutical procurement for countries with small procurement agencies* (Manila, WHO/WPRO, 2002).

## Storage/Distribution

The product quality of delivered goods has already been assured through the purchase of registered or WHO prequalified products from reliable sources. It is important that product quality is maintained throughout the supply chain all the way to the end user. By storing the products as recommended by the

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<sup>6</sup> More detailed guidance on forecasting needs is being developed.

manufacturer on the product label, product quality will be unaltered. This is also important during transport. A few products need to be refrigerated.

The stock of ARVs needs to be monitored closely to avoid both stock-outs and surplus stock, which may lead to expiry and thus wastage of expensive medicines. A system for inventory control (either manual or computerized) should exist at all places where ARVs are stored. A national inventory control system would help to redistribute stock from areas that have been overstocked to areas that are in need of certain drugs. For more details on proper storage and distribution of medicines, the reader may refer to: *Guidelines for the storage of essential medicines and other health commodities* (JSI, UNICEF, USAID, WHO; 2003. Available at [http://www.who.int/3by5/en/storage\\_pocketguide.pdf](http://www.who.int/3by5/en/storage_pocketguide.pdf)) and *Guide to good storage practices for pharmaceuticals*. Geneva, WHO Technical Report Series, No. 908, 2003, Annex 9 and *Good distribution practices (GDP) for pharmaceutical products*. Geneva, WHO Technical Report Series, No. 937, 2006, Annex 5.

### Quality assurance

As mentioned earlier, it is important to select and procure only products of adequate quality. The quality needs to be maintained throughout the lifespan of the medicines. Rather simple procedures for quality checking can be established. When the medicines arrive from the suppliers, a physical check of the items can be carried out using a simple checklist such as the *Inspection checklist for drug receipts* (Management Sciences for Health and World Health Organization, *Managing drug supply*. 2nd edition. West Hartford, CT, Kumarian Press, 1997:346). This checklist can also be used at any other time one wishes to verify product quality, though sometimes laboratory testing may be needed.

### Coordination of ARV supply management

In many countries, supply management of ARVs is done by many organizations, and not by the Ministry of Health alone. Sometimes, the activities are not coordinated and there is overlap. Therefore, it is recommended to establish a forum for regular meetings with all involved partners to identify priorities, draw on experiences and prepare plans related to ARV supply management. In collaboration with all partners, a national distribution plan for ARVs should be developed to avoid overlap and to make the best use of available resources. A nationwide patient monitoring and evaluation system linked to a nationwide inventory system for ARVs should be developed. Based on monthly reports of patient monitoring and evaluation, the needs for future procurement can be forecast and distribution plans involving all partners prepared.

For further reading on medicines supply management see: Management Sciences for Health and World Health Organization. *Managing drug supply*. 2nd edition. West Hartford, CT, Kumarian Press, 1997.

# 12

## USE OF ANTIRETROVIRAL DRUGS IN SPECIAL SITUATIONS

The tables below provide an overview on the use of antiretroviral drugs in paediatrics, during pregnancy, and concomitantly with either TB medication or methadone.

Generic name	Class	Paediatric approval	Use in pregnancy <sup>7</sup>	Recommended in persons taking TB drugs
Abacavir (ABC)	NsRTI	Yes	–	Yes
Didanosine (ddI)	NsRTI	Yes	Yes	–
Emtricitabine (FTC)	NsRTI	Yes	–	Yes
Lamivudine (3TC)	NsRTI	Yes	<b>Yes</b>	Yes
Stavudine (d4T)	NsRTI	Yes	Yes	–
Zidovudine (AZT, ZDV)	NsRTI	Yes	<b>Yes</b>	Yes
Zidovudine + lamivudine (AZT + 3TC)	NsRTI	No	Yes	Yes
Zidovudine + lamivudine + abacavir (AZT + 3TC + ABC)	NsRTI	No	–	Yes
Tenofovir (TFV)	NtRTI	No	–	–
Efavirenz (EFV)	NNRTI	Yes <sup>8</sup>	Yes <sup>9</sup>	Yes
Nevirapine (NVP)	NNRTI	Yes	<b>Yes</b> <sup>10</sup>	Yes <sup>11</sup>
Amprenavir (APV)	PI	Yes	–	–

<sup>7</sup> When drugs are in bold, 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. A combination of d4T + ddI should be avoided, because of the increased risk of fatal lactic acidosis/hepatic steatosis.

<sup>8</sup> Use only in children > 3 years of age or ≥ 10 kg in weight.

<sup>9</sup> Can be used during the second and third trimesters.

<sup>10</sup> Women with CD4 counts between 250 and 350 cells/cmm are at increased risk for NVP hypersensitivity with fatal hepatic toxicity. This applies to pregnant and nonpregnant women. NVP should be used with caution and with careful clinical and liver function monitoring in this population.

<sup>11</sup> Data on the use of NVP + rifampicin are limited and conflicting. NVP levels are reduced in the presence of rifampicin, and higher NVP doses are being evaluated. Although there are some reports of adequate viral and immunological response and acceptable toxicity, this regimen should be used only when no other options are available.

Generic name	Class	Paediatric approval	Use in pregnancy <sup>7</sup>	Recommended in persons taking TB drugs
Atazanavir (ATZ)	PI	No	-	-
Fosamprenavir (Fos-APV)	PI	No	-	-
Indinavir (IDV)	PI	No	Yes <sup>12</sup>	-
Lopinavir/ritonavir (LPV/r)	PI	Yes	-	Yes <sup>13,14</sup>
Nelfinavir (NFV)	PI	Yes	Yes	-
Ritonavir (RTV)	PI	Yes	Yes	-
Saquinavir (SQV)	PI	No	Yes <sup>12</sup>	Yes <sup>13,14</sup>
Enfuvirtide (T-20)	Entry inhibitor	Yes	-	-

Antiretroviral agent	Effect on methadone	Effect on antiretroviral agent	Comment
<b>NRTIs</b>			
Zidovudine (ZDV)	None reported No dosage adjustments necessary	Concentrations significantly increased (43%) Clinical significance unclear Adverse events possible	Monitor for ZDV adverse events  Watch for anaemia, nausea, myalgia, vomiting, asthenia, headache and bone marrow suppression in recipients
Lamivudine (3TC)	None reported	None reported	No known interactions

<sup>12</sup> Should be used in pregnancy with RTV-boosted dosages, otherwise inadequate blood levels are obtained.

<sup>13</sup> Increase dose in combination with rifampicin.

<sup>14</sup> Unboosted PIs cannot be used with rifampicin-containing regimens because PI levels are subtherapeutic. Thus, if a patient needs to switch to or is already on a PI-based regimen, LPV 400 mg/RTV 400 mg twice daily in combination with rifampicin could be considered under close clinical and laboratory monitoring to detect hepatic toxicity. Full endorsement of this regimen requires further data. Alternatively, SQV 400 mg/RTV 400 mg can be considered, with the same close clinical and laboratory monitoring, but endorsement of this PI-based regimen also requires further data. Concerns about combinations of SQV 1000 mg/r 100 mg twice daily with rifampicin include high rates of hepatic toxicity reported in a study of HIV-uninfected volunteers and the potency of the combination. The use of this and other boosted PI combinations is discouraged until further data are available.



Antiretroviral agent	Effect on methadone	Effect on antiretroviral agent	Comment
Emtricitabine (FTC)	Not studied	Not studied	No known interactions
Tenofovir (TDF)	None reported	None reported	No known interactions
Stavudine (d4T)	None reported No dosage adjustments necessary	Concentrations decreased (18–27%) Clinical significance unclear	Clinical significance of effect unclear
Abacavir (ABC)	Methadone levels mildly decreased Risk of opiate withdrawal low Dosage adjustments unlikely but some patients might require methadone dose increase	Peak concentration reduced (34%) Time to peak increased	Data sparse, although one study showed an increase of 22% in oral methadone clearance  Risk of opiate withdrawal low  Methadone dose adjustment might be needed
Didanosine (ddI) Buffered tablet Enteric-coated (EC) capsule	None reported No dosage adjustments necessary	Concentrations decreased (60%) in buffered tablet but not in EC capsule	Has only been studied with twice-daily administration of buffered tablets. Hypothesized to be due to reduced bioavailability of ddI in the setting of slower transit through the acidic environment of the stomach in patients taking methadone  Great interindividual variability in ddI pharmacokinetic data  No effect on EC capsule; EC capsule therefore preferred

Antiretroviral agent	Effect on methadone	Effect on antiretroviral agent	Comment
<b>NNRTIs</b>			
Efavirenz (EFV)	<p>Methadone concentrations significantly decreased (60%)</p> <p>Methadone withdrawal common</p> <p>Significant methadone dose increase (50%) usually required</p>	Unknown	<p>Observe closely for signs of methadone withdrawal and increase dosage as necessary</p> <p>Symptoms of withdrawal may be delayed for up to 2 or 3 weeks</p>
Nevirapine (NVP)	<p>Methadone concentrations significantly decreased (46%)</p> <p>Methadone withdrawal common</p> <p>Methadone dose increase (16%) necessary in most patients</p>	None reported	<p>In a case series of chronic methadone recipients initiating NVP, there was a need for 50–100% increases in the daily methadone doses to treat opioid withdrawal</p> <p>Withdrawal symptoms generally occur between 4 and 8 days after starting NVP</p> <p>Symptoms of withdrawal may be delayed for up to 2 or 3 weeks</p>
<b>PIs</b>			
Lopinavir/ritonavir (LPV/r)	<p>Methadone levels decreased (26–53%)</p> <p>Withdrawal might occur requiring dosage increase</p> <p>Side-effects may mimic withdrawal</p>	None reported	<p>Methadone withdrawal reported</p> <p>May require increased methadone dose</p>

Antiretroviral agent	Effect on methadone	Effect on antiretroviral agent	Comment
Saquinavir (SQV)	None reported	None reported	Studies limited, but no reported interactions
Saquinavir 1600 mg, ritonavir 100 mg  Saquinavir 1400 mg, ritonavir 400 mg  (SQV + RTV)	Methadone levels slightly reduced (SQV/RTV 1600/100 0–12%; SQV/RTV 400/400 20%)  No reported withdrawal  Methadone dosage adjustments may be necessary	Unknown	Methadone dose adjustments may be necessary; however, requires ongoing monitoring
Ritonavir (RTV)	May decrease methadone levels (37%)  Methadone dosage may need to be increased	None reported	Studies limited  Observe closely for signs of methadone withdrawal and increase dosage as necessary
Nelfinavir (NFV)	May decrease methadone levels (29–47%)  Clinical withdrawal rarely reported  Methadone dosage may need to be increased	Levels may be reduced but clinical significance unclear	Clinical withdrawal was not reported in studies in which decreased methadone concentrations were reported

# 13

## ANTIRETROVIRALS IN THE 14TH WHO MODEL LIST OF ESSENTIAL MEDICINES

Essential medicines are those that satisfy the priority health-care needs of the population.

They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.

Implementation of the concept of essential medicines is intended to be flexible and adaptable to many different situations; exactly which medicines are regarded as essential remains a national responsibility. Thus, WHO has developed a Model List of Essential Medicines<sup>15</sup>; The **core list** presents a list of minimum medicine needs for a basic health-care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. Priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment.

The complementary list comprises essential medicines for priority diseases, for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. In case of doubt, medicines may also be listed as complementary on the basis of consistently higher costs or less attractive cost-effectiveness in a variety of settings. The WHO Model List is revised every second year.

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<sup>15</sup> The WHO Model List of Essential Medicines is updated every two years. The current list can be found on: <http://www.who.int/medicines/publications/essentialmedicines/en/index.html>

## ARV medicines contained in the 14th WHO Model List of Essential Medicines

Abacavir (as sulphate) (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 sulphate) (IDV) <sup>16</sup>	Capsule 100 mg, 200 mg, 333 mg, 400 mg
Ritonavir (RTV, r) <sup>17</sup>	Capsule 100 mg; oral solution 400 mg/5 ml
Lopinavir + ritonavir (LPV/r) <sup>16</sup>	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) <sup>16</sup>	Capsule (gel-filled) 200 mg

<sup>16</sup> Not to be used as single PI; recommended use in combination with boosting dose of RTV

<sup>17</sup> RTV to be used only as “booster” for other PIs

# 14

## STORAGE CONDITIONS AND SHELF-LIFE

Like other medicines, ARVs need to be stored properly to maintain their quality throughout their shelf-lives. Manufacturers have established shelf-lives at defined storage conditions, which are printed on the container label, outer labelling or the package insert. It is important to follow the recommendations made by the manufacturers. Generally, medicines must be stored in closed containers protected from light, humidity and excessive heat. Some require refrigeration. In the subsequent sections on individual drugs, storage conditions and shelf-lives have been included as far as possible. However, it is important to check the product label as different manufacturers may have different recommendations for the same ARVs. This is due to variations in formulation (composition of ingredients), the manufacturing process and the packaging of the individual product. The general recommendations for storing medicines are as follows:

- Keep out of the reach of children.
- Store away from heat and direct light.
- Do not store in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.
- Do not keep outdated medicine or medicine no longer needed. Be sure that any discarded medicine is out of the reach of children.

The subsequent sections on individual drugs contain information on the storage conditions and shelf-lives of the various ARVs. In addition, an overview of shelf-life and recommended storage conditions can be found in Annex 3. However, this information is only indicative. It is important to always check the label, package insert and packaging for the shelf-life as it may have changed depending on additional data from stability testing by the manufacturers or reformulation of products.

# 15

## NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NsRTIs)

### Class adverse drug reactions to nucleoside reverse transcriptase inhibitors (NsRTIs)

#### Lactic acidosis/hepatic steatosis

Acute lactic acidosis and severe hepatomegaly with steatosis during NsRTI use occur at a low frequency, but with a high risk of fatality. The incidence of lactic acidosis seems to be around 1%, while an increase in serum lactate levels can be found in as many as 5–21% of patients treated with NsRTI-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 NsRTI use, pregnancy, acquired riboflavin and thiamine deficiency, and d4T use. Cases have occurred as early as one month and as late as 20 months after starting therapy. However, lactic acidosis can occur at any time in a patient receiving NRTI-based ART. 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 increase of hepatic enzymes and, in some cases, dyspnoea and/or fatigue. Evaluation shows lactic acidosis with possibly elevated creatine phosphokinase (CPK), alanine transaminase (ALT), and/or lactate dehydrogenase (LDH), low bicarbonate and increased anion gap.

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

All NsRTIs and TFV have been implicated but the syndrome is consistently reported at higher rates with the use of d4T or ddI. The combination of d4T and ddI is not recommended.

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

This adverse event has been attributed to mitochondrial toxicity caused by NsRTIs. Other clinical expressions of mitochondrial toxicity include myopathy (AZT-related), dilated cardiomyopathy (AZT), peripheral neuropathy (d4T, ddI, zalcitabine), pancreatitis (ddI, d4T, 3TC), asthenia, bone marrow suppression (AZT) and/or lipotrophy (d4T, AZT, ddI).

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

## Abacavir (ABC)

**Class:** Nucleoside reverse transcriptase inhibitor

### Available formulations

Tablets: Abacavir (as sulfate) 300 mg and 600 mg

Oral solution: Abacavir (as sulfate) 20 mg/ml

### Uses

HIV infection in combination with at least two other ARV drugs

### Contraindications

Previously demonstrated hypersensitivity to ABC. Following a hypersensitivity reaction to ABC, NEVER use any ABC-containing product. Fatal rechallenge reactions have been associated with readministration of ABC to patients with a prior history of a hypersensitivity reaction to ABC.

ABC tablets and oral solution are contraindicated in patients with moderate or severe hepatic impairment.

### Pregnancy

Should be used during pregnancy **only** if the potential benefit outweighs the risk.

### Breastfeeding

It is recommended that HIV-infected mothers do not breastfeed their infants to avoid the risk of postnatal transmission of HIV infection.

### Precautions

*Hepatic impairment (avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment):* **Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported—caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.**

*Renal impairment:* Avoid using ABC in patients with severe renal impairment.

*Hypersensitivity reactions:* **Life-threatening** hypersensitivity reactions reported—characterized by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, lethargy, malaise, headache, myalgia and renal failure; less frequently mouth ulceration, oedema, hypotension, dyspnoea, sore throat, cough, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and anaphylaxis (hypersensitivity reactions presenting as



sore throat, influenza-like illness, cough and breathlessness identified); rarely myolysis; laboratory abnormalities may include raised liver enzymes (*see below*) and creatine kinase; symptoms usually appear in the first six weeks, but may occur at any time; monitor for symptoms every two weeks for two months; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it must be carried out in a hospital setting; if ABC is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs that cause skin toxicity.

*Patient advice:* Patients should be told the importance of regular dosing (intermittent therapy may increase sensitization), how to recognize signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment. If treatment is stopped because of a serious reaction, he/she should **NEVER** take ABC again as this may, **WITHIN HOURS**, result in life-threatening symptoms that may include lowering of the blood pressure or death.

## Dosage

HIV infection (in combination with other ARV drugs), *by mouth*

*Adult:* 300 mg twice daily or 600 mg once daily

*Child:* 3 months–16 years or <37.5 kg: 8 mg/kg/dose twice daily

*Maximum dose:* > 16 years or  $\geq 37.5$  kg: 300 mg/dose twice daily

Tablets can be crushed and the contents mixed with a small amount of water or food and immediately ingested.

## Food effects

ABC can be taken with or without food.

## Metabolism

Mainly in the liver. In humans, ABC is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of ABC are metabolism by alcohol dehydrogenase (to form the 5'-carboxylic acid) and glucuronyl transferase (to form the 5'-glucuronide). The metabolites do not have antiviral activity.

## Interactions with other drugs

Rare. Pharmacokinetic properties of ABC were not altered by the addition of either 3TC or AZT or the combination of 3TC and AZT. No clinically

significant changes to 3TC or AZT pharmacokinetics were observed following concomitant administration of ABC.

Ethanol decreases the elimination of ABC causing an increase in overall exposure (care must be taken when co-administered with RTV or LPV oral solutions in children).

ABC increases the levels of APV.

ABC decreases the levels of methadone (in some patients) but adjustment of methadone dose is usually not required. Monitor patients for signs of methadone withdrawal.

Methadone decreases ABC levels by 34% but no ABC dose adjustment is recommended.

### Adverse effects

Hypersensitivity reactions (*see above*), nausea, vomiting, diarrhoea, anorexia, lethargy, fatigue, fever, headache, pancreatitis, lactic acidosis/hepatic steatosis (*see* “Class adverse drug reactions”, p. 29); rash and gastrointestinal disturbances are more common in children.

Hypersensitivity to ABC was reported in approximately 8% of 2670 patients ( $n=206$ ) in 9 clinical trials (range: 2–9%).

### Storage

*Tablets:* Store at room temperature (15–30°C). If stored as recommended, shelf-life is 3 years.

*Oral solution:* Store at room temperature (15–30°C). DO NOT FREEZE. May be refrigerated. If stored as recommended, shelf-life is 2 years.

## Didanosine (ddI)

**Class:** Nucleoside reverse transcriptase inhibitor

### Available formulations

- Oral suspension paediatric powder/water: 10 mg/ml. In many countries, it needs to be made up with additional antacid.
- Chewable/dispersible buffered tablets: 25, 50, 100, 150, 200 mg (at least 2 tablets should be administered each time to ensure adequate buffering capacity).
- Enteric-coated (EC) capsules: 125, 200, 250, 400 mg.

### Uses

HIV infection in adults or children >6 months of age in combination with at least two other ARVs.

### Contraindications

Previously demonstrated clinically significant hypersensitivity to any of the components of the products.

### Pregnancy

It is not known if ddI can harm a human fetus. However, pregnant women have experienced serious side-effects when taking ddI in combination with d4T and other ARVs. ddI should be used during pregnancy only if the potential benefit justifies the potential risk.

### Breastfeeding

It is not known whether ddI is excreted in human milk. Because many medicines are excreted in human milk and because of the potential for serious adverse reactions from ddI in nursing infants, mothers should be instructed to discontinue nursing when taking ddI.

### Precautions

Dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur.

*Pancreatitis:* If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if asymptomatic) suspend treatment until the diagnosis of pancreatitis is excluded; on return to normal values re-initiate treatment only if essential (using low dose and increasing gradually if appropriate). Whenever possible, avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example, intravenous pentamidine isetionate); monitor

closely if concomitant therapy unavoidable. Since significant increase in the levels of triglycerides cause pancreatitis, monitor closely if elevated.

*Hepatic disease:* Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; therefore, caution in liver disease, excessive alcohol intake, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

*Peripheral neuropathy:* Patients with a history of peripheral neuropathy or those receiving ddI in combination with other neurotoxic drugs may be at increased risk for developing peripheral neuropathy (see “Adverse reactions”). These patients should be carefully observed.

## Dosage

HIV infection (in combination with other ARVs), *by mouth*

*Adult:* Body weight 60 kg and < 60 kg: 250 mg once daily; body weight > 60 kg: 400 mg once daily

*Child:* < 3 months, 50 mg/m<sup>2</sup> twice daily; 3 months–13 years, 90–120 mg/m<sup>2</sup>/dose twice daily or 240 mg/m<sup>2</sup>/dose once daily

*Maximum dose:* ≥ 13 years or > 60 kg: 200 mg/dose twice daily or 400 mg once daily

Enteric-coated beadlets in capsules can be sprinkled on a small amount of food.

If powder for oral solution is not available and to ensure sufficient antacid from tablets containing antacid, each dose to be taken as 2 tablets (**child** < 1 year 1 tablet) chewed thoroughly, crushed or dispersed in water; tablets should be taken at least 1 hour before food or on an empty stomach. (Two tablets should be thoroughly chewed, manually crushed, or dispersed in at least 30 ml of water prior to consumption. To disperse tablets, add 2 tablets to at least 30 ml of drinking water. Stir until a uniform dispersion forms, and drink the entire dispersion immediately. If additional flavouring is desired, the dispersion may be diluted with 30 ml of clear apple juice. Stir the further diluted dispersion just before consumption. When a one-tablet dose is required for a child, the volume of water for dispersion should be 15 ml. Fifteen ml of clear apple juice may be added to the dispersion as a flavouring, as described above.)

*Preparation of solution:* Prior to dispensing, the pharmacist must constitute dry powder with purified water, USP, to an initial concentration of 20 mg/ml and immediately mix the resulting solution with antacid to a final concentration of 10 mg/ml as follows:

*20 mg/ml initial solution:* Reconstitute the product to 20 mg/ml by adding 100 ml or 200 ml of purified water, USP, to the 2 g or 4 g of ddI powder, respectively, in the product bottle.

*10 mg/ml final admixture:* Immediately mix one part of the 20 mg/ml initial solution with one part of a liquid antacid containing aluminium hydroxide, magnesium hydroxide and simethicone.

*Suspension for a final dispensing concentration of 10 mg ddI per ml:* For patient home use, the admixture should be dispensed in appropriately sized, flint-glass or plastic (HDPE, PET or PETG) bottles with child-resistant closures. This admixture is stable for 30 days under refrigeration (2–8°C).

Instruct the patient to shake the admixture thoroughly prior to use and to store the tightly closed container in the refrigerator (2–8°C) up to 30 days.

### Food effect

Should be taken on an empty stomach; at least half an hour before or two hours after a meal.

### Metabolism

It is presumed that the metabolism of ddI in humans occurs by the same pathways responsible for the elimination of endogenous purines.

### Interactions

Rare

Do not administer d4T with ddI due to the risk of acute lactic acidosis and death.

*Contraindicated drugs (ddI not to be taken with these drugs):* Allopurinol, tenofovir (TFV)—inferior virological and CD4 count responses and drug interactions.

ddI levels are decreased by methadone, except when enteric-coated ddI is used; hence enteric-coated ddI preparations are preferable when ddI is co-administered with methadone.

ddI levels are increased by oral ganciclovir; TFV; ddI and TDF should preferably not be co-administered.

ddI<sup>18</sup> decreases the absorption of IDV, RTV, fluoroquinolones, dapson, itraconazole, ketoconazole (separate administration: at least two hours before or after ddI).

<sup>18</sup> Didanosine in the form of tablets or paediatric powder

## Adverse effects

Lactic acidosis/hepatic steatosis (*see* “Class adverse drug reactions”, p. 29); pancreatitis (*see also* under “Precautions”); peripheral neuropathy especially in advanced HIV infection—suspend (reduced dose may be tolerated when symptoms resolve); hyperuricaemia (suspend treatment if marked increase in serum uric acid levels); diarrhoea (occasionally serious); also reported are nausea, vomiting, dry mouth, asthenia, headache, hypersensitivity reactions, retinal and optic nerve changes (especially in children), diabetes mellitus, raised liver enzymes (*see also* under “Precautions”), liver failure.

## Storage

*Enteric-coated (gastro-resistant) capsules:* The capsules should be stored in tightly closed containers at room temperature (15–30°C); The shelf-life is 24 months.

The powder for oral solution should be stored at room temperature (15–30°C). The ddI reconstituted mixture may be stored for up to 30 days in a refrigerator (2–8°C). Discard any unused portion after 30 days.

For chewable tablets and powder for oral solution, see the labelling and package inserts.

## Emtricitabine (FTC)

**Class:** Nucleoside reverse transcriptase inhibitor (NsRTI)

Available formulations

Tablet: 200 mg

Capsules: 200 mg

Oral solution: 10 mg/ml

### Uses

For the treatment of HIV-infected adults in combination with other ARVs. It can be used in children > 3 months of age as an alternative to 3TC.

### Contraindications

Previously demonstrated hypersensitivity to any of the components of the product.

### Pregnancy

Studies in mice and rabbits have shown that FTC readily crosses the placenta. No evidence of embryo–fetal toxicity or teratogenicity was observed in pregnant mice or rabbits given oral doses of FTC up to 1000 mg/kg/day (52 and 130 times the clinical exposure based on area under the curve [AUC], respectively). Impaired weight gain observed in pregnant rabbits at doses  $\geq 300$  mg/kg/day was not associated with any adverse fetal effects (at least 33 times the clinical exposure based on AUC). There are, however, no adequate and well-controlled studies in pregnant women.

### Breastfeeding

No developmental toxicity was noted postnatally in the offspring of mice given oral FTC up to 1000 mg/kg/day (52 times the clinical exposure based on AUC) from gestation through lactation. Impaired weight gain observed in lactating mice at the 1000 mg/kg/day dose was not associated with any adverse events on pup survival, developmental or reproductive parameters.

It is not known whether FTC is excreted in animal or human milk. Because of the potential for HIV transmission and for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving FTC.

### Precautions

*Lactic acidosis/severe hepatomegaly with steatosis:* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with

the use of nucleoside analogues alone or in combination, including FTC and other ARVs. A majority of these cases have been in women. Obesity and prolonged nucleoside exposure may be risk factors. However, cases have also been reported in patients with no known risk factors. Treatment with FTC should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity (which may include hepatomegaly and steatosis even in the absence of marked increase in transaminase levels).

*Patients co-infected with HIV and hepatitis B virus:* It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating ART. FTC is not indicated for the treatment of chronic HBV infection, and the safety and efficacy of FTC have not been established in patients co-infected with HBV and HIV.

Severe, acute exacerbations of hepatitis B have been reported in patients after discontinuation of FTC. Hepatic function should be monitored closely with both clinical and laboratory follow up for at least several months in patients who discontinue FTC and are co-infected with HIV and HBV. If appropriate, initiation of anti-hepatitis B therapy may be warranted.

## Dosage

*Adults (> 18 years):* 200 mg tablet or capsule taken once daily or 240 mg (24 ml) oral solution administered once daily orally.

*Children (3 months through 17 years):* 200 mg tablets or capsules. For children weighing > 33 kg who can swallow an intact capsule, one 200 mg capsule or tablet can be administered once daily orally.

*Oral solution:* 6 mg/kg up to a maximum of 240 mg (24 ml) administered once daily orally.

## Food effect

Can be taken with or without food.

## Metabolism

Following oral administration of <sup>14</sup>C-emtricitabine, complete recovery of the dose was achieved in the urine (~86%) and feces (~14%). Thirteen per cent (13%) of the dose was recovered in urine as three putative metabolites. The biotransformation of FTC includes the oxidation of the thiol moiety to form the 3'-sulfoxide diastereomers (~9% of the dose) and conjugation with glucuronic acid to form the 2'-O-glucuronide (~4% of the dose). No other metabolites were identifiable.



## Interactions

The potential for drug interactions with FTC has been studied in combination with IDV, ZDV, d4T, TDF and famciclovir. There were no clinically significant drug interactions for any of these drugs.

Based on the results of in vitro experiments and the known elimination pathways of FTC, the potential for CYP450-mediated interactions involving FTC with other medicinal products is low.

## Adverse effects

Assessment of adverse reactions is based on data from three studies in adults (n=1479) and three paediatric studies (n=169). In the adult studies, 1039 treatment-naïve and 440 treatment-experienced patients received FTC (n=814) or a comparator medicinal product (n=665) for 48 weeks in combination with other ARV medicinal products. In the three paediatric studies, treatment-naïve (n=123) and treatment-experienced (n=46) paediatric patients aged 4 months–18 years were treated with FTC in combination with other ARV agents.

The adverse reactions with suspected (at least possible) relationship to treatment in adults are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (> 1/10) or common (> 1/100, < 1/10).

*Blood and the lymphatic system disorders:* Common—neutropenia

*Metabolism and nutrition disorders:* Common—hypertriglyceridaemia, hyperglycaemia.

Lactic acidosis, usually associated with hepatic steatosis, has been reported with the use of nucleoside analogues (see “Class adverse drug reactions”, p. 29).

*Nervous system disorders:* Very common—headache

Common—dizziness, asthenia, insomnia, abnormal dreams

*Gastrointestinal disorders:* Very common—diarrhoea, nausea

Common—vomiting, dyspepsia, abdominal pain, raised serum lipase, raised amylase including pancreatic amylase

*Hepatobiliary disorders:* Common—raised serum aspartate aminotransferase (AST) and/or raised serum ALT, hyperbilirubinaemia

*Skin and subcutaneous tissue disorders:* Common—pruritus, maculopapular rash, urticaria, vesiculobullous rash, pustular rash, allergic reaction, skin discolouration (hyperpigmentation).

*Musculoskeletal, connective tissue and bone disorders:* Very common—elevated creatine kinase

*General disorders and administration site conditions:* Common—pain

### **Storage**

*Tablets (film-coated):* See labelling

*200 mg capsules:* Store at room temperature (15–30°C); the shelf-life is 2 years.

*10 mg/ml oral solution:* Store in a refrigerator (2–8°C). The shelf-life is 3 years.

After first opening the bottle, the shelf-life is 45 days. Do not store the opened bottle above 25°C.

## Lamivudine (3TC)

**Class:** Nucleoside reverse transcriptase inhibitor (NsRTI)

### Available formulations

*Oral suspension:* 10 mg/ml

*Tablets:* 100, 150, 300 mg

### Uses

HIV infection in combination with at least two other ARV drugs.

### Contraindications

Known hypersensitivity to 3TC or to any ingredient of the products.

### Pregnancy

Limited data are available on the safety of 3TC in human pregnancy. Studies in humans have confirmed that 3TC crosses the placenta. 3TC concentrations in infant serum at birth were similar to those in maternal and cord serum at delivery.

Reproductive studies in animals have not shown evidence of teratogenicity, and showed no effect on male or female fertility. 3TC produced small increases in early embryonic loss when administered to pregnant rabbits at exposure levels comparable with those achieved in man. However, there was no evidence of embryonic loss in rats at exposure levels of approximately 60 times the clinical exposure (based on  $C_{max}$ ).

Use in pregnancy should be considered only if the benefit outweighs the risk. Although the results of animal studies are not always predictive of human response, findings in the rabbit suggest a potential risk of early embryonic loss. Consequently, 3TC administration is not recommended during the first three months of pregnancy.

For patients on treatment with 3TC and who subsequently become pregnant, consideration should be given to the possibility of a recurrence of hepatitis on discontinuation of 3TC.

### Breastfeeding

Following oral administration, 3TC was excreted in human breast milk at similar concentrations to those found in serum (range 1–8  $\mu\text{g/ml}$ ).

Data from animal studies in which neonatal rats received 3TC at much higher concentrations via maternal milk suggest that the concentrations of 3TC in human breast milk are unlikely to produce toxicity in breastfed infants.

Because of the potential for HIV transmission, mothers should be instructed not to breastfeed.

### Dosage

*Adults:* 150 mg (tablets) twice daily or 300 mg once daily

Infants < 30 days: 2 mg/kg/dose twice daily

Children  $\geq$  30 days or < 60 kg: 4 mg/kg/dose twice daily (maximum 150 mg twice daily)

Tablets can be crushed and mixed with a small amount water or food and taken immediately.

### Food effect

Can be taken with or without food.

### Metabolism

It is eliminated unchanged through renal excretion.

### Precautions

#### *Renal impairment*

*Hepatic disease:* Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; therefore, caution (particularly in obese women) in liver disease, liver enzyme abnormalities, or risk factors for liver disease; suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis. Recurrent hepatitis in patients with chronic hepatitis B infection may occur on discontinuation of 3TC.

### Interactions

Rare

Trimethoprim/sulfamethoxazole (TMP/SMX) increases the blood levels of 3TC.

Do not administer with zalcitabine due to possible antagonism.

A modest increase in  $C_{\max}$  (28%) was observed for AZT when administered with 3TC.

### Adverse effects

Nausea, vomiting, diarrhoea, abdominal pain; cough; headache, fatigue, insomnia; malaise, fever, rash, alopecia, muscle disorders; nasal symptoms; peripheral neuropathy reported; rarely pancreatitis (discontinue); neutropenia, anaemia, thrombocytopenia and red cell aplasia; lactic acidosis/hepatic steatosis

(see “Class adverse drug reactions”, p. 29); raised liver enzymes and serum amylase reported.

### Storage

Stored at room temperature (15–30°C). The shelf-lives are:

*Tablets:* 2 years or longer depending on the manufacturer (see labelling)

*Oral powder:* 2 years

*Film-coated tablets:* 3 years<sup>19</sup>

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<sup>19</sup> Source: European Agency for Evaluation of Medicinal Products (EMA)

## Stavudine (d4T)

**Class:** Nucleoside reverse transcriptase inhibitor (N<sub>s</sub>RTI)

### Available formulations

*Capsules:* 15, 20, 30 and 40 mg

*Extended-release capsules (d4T XR):* 37.5 mg, 50 mg, 75 mg and 100 mg

*Powder for oral solution:* d4T 200 mg. The reconstituted solution contains 1 mg of d4T per ml.

### Preparation of solution

Constitute with water to a 200 ml deliverable volume solution (d4T concentration of 1 mg/ml):

Add 202 ml of water to the original bottle (when the patient makes up the solution, they should be instructed to fill to the mark). Replace the cap.

Shake the bottle well until the powder dissolves completely. The solution may remain slightly hazy.

Dispense the solution with the measuring cup provided, or for doses less than 10 ml, dispense with a syringe. The patient should be instructed to shake the bottle well before measuring each dose.

### Uses

HIV infection in combination with at least two other ARV drugs. d4T is indicated for the treatment of HIV-infected patients (>5 months of age) for whom AZT therapy is not, or is no longer, appropriate.

### Contraindications

Contraindicated in patients with hypersensitivity to d4T or to any component of the formulations.

### Pregnancy

There are no adequate and well-controlled studies of d4T in pregnant women. d4T should be used in pregnancy only if the potential benefit justifies the potential risk. Fatal lactic acidosis has been reported in pregnant women who received a combination of d4T and ddI with other ARVs. It is not known if pregnancy augments the risk of lactic acidosis/hepatic steatosis syndrome reported in nonpregnant individuals receiving nucleoside analogues. The combination of d4T and ddI should be used with caution during pregnancy and is recommended only if the potential benefit clearly outweighs the potential

risk. Health-care providers caring for HIV-infected pregnant women receiving d4T should be aware of the need for early diagnosis of lactic acidosis/hepatic steatosis syndrome.

A study in rats showed that d4T is transferred to the fetus through the placenta. The concentration in fetal tissue was approximately one-half that of the maternal plasma. Animal reproduction studies are not always predictive of human response.

### Breastfeeding

It is recommended that HIV-infected women do not breastfeed under any circumstances in order to avoid transmission of HIV.

The data available on d4T excretion in human breast milk are insufficient to assess the risk to the infant. Studies in lactating rats showed that d4T is excreted in breast milk. Therefore, mothers should be instructed to discontinue breastfeeding prior to receiving d4T.

### Precautions

History of peripheral neuropathy (*see below*); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; hepatic disease (*see below*); renal impairment.

*Peripheral neuropathy:* Suspend if peripheral neuropathy develops—characterized by persistent numbness, tingling or pain in feet or hands; if symptoms resolve satisfactorily on withdrawal, and if d4T needs to be continued, resume treatment at half the previous dose.

*Hepatic disease:* Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; therefore, caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women); suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

### Dosage

*Adults (12 years of age or older):* The recommended starting dosage based on body weight is as follows:

40 mg twice daily for patients  $\geq 60$  kg

30 mg twice daily for patients  $< 60$  kg

The recommended dose of d4T XR is 100 mg once daily for individuals weighing at least 60 kg and 75 mg once daily for individuals weighing  $< 60$  kg.

*Children:* 1 mg/kg/dose twice daily for patients < 30 kg  
30 mg twice daily for patients ≥ 30 to < 60 kg

*Maximum dose for those > 60 kg:* 40 mg/dose twice daily

When d4T is taken with food, peak plasma levels are altered, but overall exposure is unchanged. The clinical significance of this is unknown.

### Food effect

Can be taken with or without food.

### Metabolism

The metabolism of d4T has not been elucidated in humans. Studies in monkeys indicate that approximately 50% is excreted unchanged in the urine; most of the remainder is hydrolysed to thymine and sugar.

### Interactions

Since d4T is actively secreted by the renal tubules, interactions with other actively secreted medicinal products are possible, e.g. with trimethoprim. No clinically relevant pharmacokinetic interaction has, however, been seen with 3TC.

AZT and d4T are phosphorylated by the cellular enzyme thymidine kinase, which preferentially phosphorylates AZT, thereby decreasing the phosphorylation of d4T to its active triphosphate form. **AZT is therefore not recommended to be used in combination with d4T.**

In vitro studies indicate that the activation of d4T is inhibited by doxorubicin and ribavirin but not by other medicinal products used in HIV infection which are similarly phosphorylated, e.g. ddI, zalcitabine, ganciclovir and foscarnet. The influence of d4T on the phosphorylation kinetics of nucleoside analogues other than AZT has not been investigated.

It is postulated that AZT may competitively inhibit the intracellular phosphorylation of d4T. Therefore, the use of AZT in combination with d4T is not recommended.

d4T does not inhibit the major cytochrome P450 isoforms CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4; therefore, it is unlikely that clinically significant drug interactions will occur with drugs metabolized through these pathways.

Because d4T is not protein bound, it is not expected to affect the pharmacokinetics of protein-bound drugs.

There have been no formal interaction studies with other medicinal products.



If possible, the combined use of d4T and ddI is not recommended due to the risk of acute lactic acidosis and death.

d4T levels are decreased by methadone (*see also* Chapter 12).

### Adverse effects

*Adults:* Extensive safety experience is available for d4T immediate-release formulations used as monotherapy and in combination regimens. Many of the serious undesirable effects with d4T were consistent with the course of HIV infection or with the side-effects of concomitant therapies. The safety of d4T prolonged-release hard capsules has been compared to d4T immediate-release formulations, each in combination with EFV and 3TC, in two randomized, double-blind clinical trials. The safety profile of the prolonged-release capsule was not substantially different from that of the immediate-release form.

*Peripheral neuropathy:* In two clinical trials comparing d4T immediate-release with d4T prolonged-release, the frequency of peripheral neurological symptoms was 19% (6% for moderate-to-severe symptoms) for d4T immediate-release, with a rate of discontinuation due to neuropathy of 2%. Dose-related peripheral neuropathy requiring dose modification occurred in monotherapy trials with d4T immediate-release. The patients usually experienced resolution of symptoms after dose reduction or interruption of treatment.

*Pancreatitis:* Pancreatitis, occasionally fatal, has been reported in up to 2–3% of patients enrolled in monotherapy clinical studies). Pancreatitis was reported in <1% of patients on d4T in studies comparing d4T prolonged-release with d4T immediate-release capsules.

*Lactic acidosis:* Cases of lactic acidosis, sometimes fatal, usually associated with severe hepatomegaly and hepatic steatosis, have been reported with the use of nucleoside analogues (*see* “Class adverse drug reactions”, p. 29).

Hepatitis or liver failure, which was fatal in some cases, has been reported with the use of d4T and with other nucleoside analogues.

*Immune reconstitution inflammatory syndrome (IRIS):* In HIV-infected patients with severe immune deficiency at the time of initiation of ART, an inflammatory reaction to asymptomatic or residual opportunistic infections (OIs) may arise.

*Lipodystrophy and metabolic abnormalities:* In HIV-infected patients, ART has been associated with redistribution of body fat (lipodystrophy) including the loss of peripheral and facial subcutaneous fat, increased intra-abdominal and visceral fat, breast hypertrophy and dorsocervical fat accumulation (buffalo hump).

ART has been associated with metabolic abnormalities such as hypertriglyceridaemia, hypercholesterolaemia, insulin resistance, hyperglycaemia and hyperlactataemia.

The frequency of adverse reactions listed below is defined using the following convention:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$ ,  $< 1/10$ ); uncommon ( $\geq 1/1000$ ,  $< 1/100$ ); rare ( $\geq 1/10\ 000$ ,  $< 1/1000$ ); very rare ( $< 1/10\ 000$ ).

Undesirable effects (moderate to severe) were reported in 467 patients treated with d4T immediate-release in combination with 3TC and EFV in two randomized clinical trials and an ongoing long-term follow-up study (total follow up: median 56 weeks ranging up to 119 weeks). The following undesirable effects considered possibly related to the study regimen based on investigators' attribution have been identified:

*Endocrine disorders:* Uncommon—gynaecomastia

*Gastrointestinal disorders:* Common—diarrhoea, nausea, abdominal pain, dyspepsia

Uncommon—pancreatitis, vomiting

*General disorders and administration site conditions:* Common—fatigue

Uncommon—asthenia

*Hepatobiliary disorders:* Uncommon—hepatitis or jaundice

*Metabolism and nutrition disorders:* Common—lipodystrophy

Uncommon—lactic acidosis (in some cases involving motor weakness), anorexia

*Musculoskeletal, connective tissue and bone disorders:* Uncommon—arthralgia, myalgia

*Nervous system disorders:* Common—peripheral neurological symptoms including peripheral neuropathy, paraesthesia and peripheral neuritis; dizziness; abnormal dreams; headache, insomnia; abnormal thinking; somnolence

*Psychiatric disorders:* Common—depression

Uncommon—anxiety, emotional lability

*Skin and subcutaneous disorders:* Common—rash, pruritus

Uncommon—urticaria

The discontinuation rate due to undesirable events was 7% for patients treated with d4T immediate-release.

## Storage

d4T capsules should be stored in tightly closed containers at room temperature (15–30°C). The shelf-life is 2 years.

d4T powder for oral solution should be stored and protected from excessive moisture in tightly closed bottles at room temperature (15–30°C). The shelf-life is 2 years.

After reconstitution, the oral solution may be stored in the original bottle with the lid tightly closed for up to 30 days under refrigeration (2–8°C). Discard any unused portion after 30 days.

Extended-release capsules should be stored in tightly closed containers at room temperature (15–30°C). The shelf-life is 2 years.

## Zidovudine (AZT, ADV)

**Class:** Nucleoside reverse transcriptase inhibitor (N<sub>s</sub>RTI)

### Available formulations

- *Oral solution:* 10 mg/ml
- *Capsules:* 100, 250 and 300 mg
- *Tablets:* 300 mg
- *IV solution:* (concentrate for solution for infusion) 10 mg/ml (only used in special circumstances)

### Uses

AZT is indicated in combination with other ARVs for the treatment of HIV infection in adults and children.

AZT is indicated for use in HIV-positive pregnant women and their newborn infants as it has been shown to reduce the rate of maternal–fetal transmission of HIV.

### Contraindications

AZT is contraindicated in patients known to be hypersensitive to AZT, or to any of the components of the formulations.

AZT should not be given to patients with abnormally low neutrophil counts ( $<0.75 \times 10^9$ /litre) or abnormally low haemoglobin levels ( $<7.5$  g/dl or 4.65 mmol/l) (see “Warnings and precautions”).

### Pregnancy

AZT has been shown to cross the placenta in humans. It is recommended that, where possible, women infected with HIV do not breastfeed their infants to avoid transmission of HIV. Given the limited data available on the general use of AZT in pregnancy, the use of AZT before the 14th week of gestation should be considered only when the potential benefit to the mother outweighs the risk to the fetus.

### Breastfeeding

Because of both the potential for HIV transmission and for serious adverse reactions in nursing infants, mothers on AZT should be instructed not to breastfeed. After administration of a single dose of 200 mg AZT to HIV-infected women, the mean concentration of AZT was similar in human milk and serum. Therefore, as AZT and the virus pass into breast

milk it is recommended that mothers taking AZT do not breastfeed their infants.

### Precautions

Haematological toxicity; vitamin B<sub>12</sub> deficiency (increased risk of neutropenia); reduce dose or interrupt treatment according to product literature if anaemia or myelosuppression; renal impairment; hepatic impairment; risk of lactic acidosis.

*Hepatic disease:* Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; therefore, caution in liver disease, liver enzyme abnormalities, or risk factors for liver disease (particularly in obese women), suspend or discontinue if deterioration in liver function tests, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis.

### Dosage

*Adults:* 250 mg or 300 mg twice daily

*Children:* < 6 weeks: 4 mg/kg/dose twice daily  
6 weeks–13 years: 180–240 mg/m<sup>2</sup>/dose twice daily

*Maximum dose:* ≥ 13 years: 300 mg/dose twice daily

*Patients temporarily unable to take AZT by mouth:* By intravenous infusion over 1 hour, **adult** 1–2 mg/kg every 4 hours (approximating to 1.5–3 mg/kg every 4 hours by mouth) usually for not more than 2 weeks; child 80–160 mg/m<sup>2</sup> every 6 hours (120 mg/m<sup>2</sup> every 6 hours approximates to 180 mg/m<sup>2</sup> every 6 hours by mouth)<sup>20</sup>.

*Dosage for the prevention of maternal–fetal transmission:* The recommended dose of AZT for pregnant women from week 36 of gestation is 300 mg AZT twice daily orally until the onset of labour, and 300 mg AZT orally every three hours from the onset of labour until delivery.

### Food effect

Can be taken with or without food.

### Metabolism

AZT is primarily eliminated by hepatic conjugation to an inactive glucuronidated metabolite. Active substances which are primarily eliminated by hepatic metabolism especially via glucuronidation may have the potential to inhibit the metabolism of AZT.

<sup>20</sup> See Chapter 7 for calculation of body surface area.

## Interactions

**3TC:** A modest increase in  $C_{\max}$  (28%) was observed for AZT when administered with 3TC; however, overall exposure (AUC) was not significantly altered. AZT has no effect on the pharmacokinetics of 3TC.

**Phenytoin:** Phenytoin blood levels have been reported to be low in some patients receiving AZT, while in one patient a high level was noted. These observations suggest that phenytoin levels should be carefully monitored in patients receiving both medicinal products.

**Probenecid:** Limited data suggest that probenecid increases the mean half-life and area under the plasma concentration–time curve of AZT by decreasing glucuronidation. Renal excretion of the glucuronide (and possibly AZT itself) is reduced in the presence of probenecid.

**Ribavirin:** The nucleoside analogue ribavirin antagonizes the *in vitro* antiviral activity of AZT and so concomitant use of this active substance should be avoided.

**Rifampicin:** Limited data suggest that co-administration of AZT and rifampicin decreases the AUC of AZT by  $48\% \pm 34\%$ . However, the clinical significance of this is unknown.

**d4T:** AZT may inhibit the intracellular phosphorylation of d4T when the two medicinal products are used concurrently. d4T is therefore not recommended to be used in combination with AZT.

Methadone levels are not affected by AZT. Methadone increases AZT concentrations by 43% (*see also* Chapter 12).

Monitor for adverse events of AZT, including anaemia, neutropenia, nausea, myalgia, vomiting and headache. Dose adjustment of AZT is not recommended.

**Miscellaneous:** Other active substances including, but not limited to, aspirin, codeine, morphine, methadone, indomethacin, ketoprofen, naproxen, oxazepam, lorazepam, cimetidine, clofibrate, dapsone and isoprinosine may alter the metabolism of AZT by competitively inhibiting glucuronidation or directly inhibiting hepatic microsomal metabolism. Careful thought should be given to the possibilities of interactions before using such medicinal products, particularly for long-term therapy, in combination with AZT.

Concomitant treatment, especially acute therapy, with potentially nephrotoxic or myelosuppressive medicinal products (e.g. systemic pentamidine, dapsone, pyrimethamine, co-trimoxazole, amphotericin, flucytosine, ganciclovir, interferon, vincristine, vinblastine and doxorubicin) may also increase the

risk of adverse reactions to AZT. If concomitant therapy with any of these medicinal products is necessary then extra care should be taken to monitor renal function and haematological parameters and, if required, the dosage of one or more agents should be reduced.

Since some patients receiving AZT may continue to experience opportunistic infections, concomitant use of prophylactic antimicrobial therapy may have to be considered. Such prophylaxis has included co-trimoxazole, aerosolized pentamidine, pyrimethamine and aciclovir. Limited data from clinical trials do not indicate a significantly increased risk of adverse reactions to AZT with these medicinal products.

### Adverse effects

*Blood and lymphatic system disorders:* Common—anaemia (which may require transfusions), neutropenia and leucopenia.

These occur more frequently at higher dosages (1200–1500 mg/day) and in patients with advanced HIV disease (especially when there is poor bone marrow reserve prior to treatment), and particularly in patients with CD4 cell counts < 100/mm<sup>3</sup>. Dosage reduction or cessation of therapy may become necessary. The incidence of neutropenia was also increased in those patients whose neutrophil counts, haemoglobin levels and serum vitamin B<sub>12</sub> levels were low at the start of AZT therapy.

*Metabolism and nutrition disorders:* Common—hyperlactataemia

Rare—lactic acidosis/hepatic steatosis (*see* “Class adverse drug reactions”, p. 29), anorexia, redistribution/accumulation of body fat (*see* “Special warnings and special precautions for use”). The incidence of this event is dependent on multiple factors including the particular ARV drug combination.

Other adverse effects include nausea and vomiting, abdominal pain, dyspepsia, diarrhoea, flatulence, taste disturbance, pancreatitis, liver disorders including fatty change and raised bilirubin and liver enzymes (*see* “Hepatic disease” above); chest pain, dyspnoea, cough; influenza-like symptoms, headache, fever, paraesthesia, neuropathy, convulsions, dizziness, somnolence, insomnia, anxiety, depression, loss of mental acuity, malaise, anorexia, asthenia, myopathy, myalgia; pancytopenia, thrombocytopenia; gynaecomastia; urinary frequency; rash, pruritus, pigmentation of the nails, skin and oral mucosa.

### Storage

*Capsules 100 mg:* Store at room temperature (15–30°C). Keep dry. Protect from light. Shelf-life: 3–5 years depending on the manufacturer. Check the labelling.

*Tablets:* Store at room temperature (15–30° C). The shelf-life is 2–3 years, depending on the manufacturer. Check the labelling.

*Oral solution/syrup:* Store at room temperature (15–30° C). The shelf-life is 2–3 years, depending on the manufacturer. Check the labelling.

*IV solution:* (Concentrate for solution for infusion) 10 mg/ml: Store at room temperature (15–30° C). The shelf-life is 3 years.



# 16

## NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS NtRTIs

### Tenofovir (TFV)

**Class:** Nucleotide reverse transcriptase inhibitor (NtRTI)

#### Available formulations

Tablets: 300 mg. Each film-coated tablet contains 300 mg of tenofovir disoproxil as fumarate (TDF), equivalent to 245 mg of tenofovir disoproxil, or 136 mg of TFV.

#### Uses

For treatment of HIV-infected adults in combination with other ARVs.

#### Contraindications

Known hypersensitivity to TFV, TDF, or to any of the excipients (inactive ingredients) in the tablets.

TFV must not be administered to children or adolescents until further data become available describing the safety and efficacy of TFV in patients < 18 years of age.

#### Pregnancy

Reproduction studies have been performed in rats and rabbits at doses up to 14–19 times the human dose based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to TFV. There are however no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, TDF should be used during pregnancy only if clearly needed.

#### Breastfeeding

In animal studies TFV was excreted in milk after oral administration of TDF (rats) and after subcutaneous administration of TFV base (nonhuman primates). It is not known whether TFV is excreted in human milk. To avoid transmission of HIV to the infant, it is recommended that HIV-infected women do not breastfeed their infants.

#### Precautions

*Impaired renal function:* Dosing interval adjustment (300 mg every 2nd day) is required in all patients with creatinine clearance < 50 ml/min. The proposed

dose interval modifications are based on limited data and may not be optimal. The safety and efficacy of these dosing interval adjustment guidelines have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients.

*Lactic acidosis/severe hepatomegaly with steatosis:* Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of ARV nucleoside analogues alone or in combination, including TDF, in the treatment of HIV infection. A majority of these cases have been reported in women. Preclinical and clinical data suggest that the risk of occurrence of lactic acidosis, a class effect of nucleoside analogues, is low for TDF. However, as TFV is structurally related to the nucleoside analogues, this risk cannot be excluded. Caution should be exercised when administering TFV to any patient, and particularly to those with known risk factors for liver disease. Treatment with TFV should be suspended in any patient who develops clinical or laboratory findings suggestive of lactic acidosis or hepatotoxicity.

## Dosage

*Adults:* 300 mg once daily  
300 mg every 2nd day in patients with renal impairment

TFV must not be administered to children or adolescents until further data become available describing the safety and efficacy of TFV in patients < 18 years of age.

## Paediatric use

The safety and effectiveness of TFV in paediatric patients has not been established.

## Food effect

Should be taken with food.

## Metabolism

It is eliminated mainly unchanged in the urine.

## Interactions

Minimal inhibition of CYP1A (cytochrome P450 1A isoform).

If ddI or antacids are administered, they should be taken at least two hours apart.

TFV increases the levels of ddI; hence TFV is preferably not co-administered with ddI.

TFV levels are increased by LPV/r.

TFV decreases the levels of LPV and RTV.

TFV affects the pharmacokinetics of ATZ. TFV should only be administered with boosted ATZ (ATZ 300 mg/RTV 100 mg). The safety and efficacy of this regimen has been substantiated over 48 weeks in a clinical study.

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

### Adverse effects

Headache, high blood pressure, or a general sense of feeling ill. These side-effects are likely to get better or even disappear over time.

The most common side-effects of TFV are nausea, vomiting and loss of appetite. In some people, TFV can increase the levels of creatinine and transaminases. These are enzymes related to the kidneys and liver. High levels can indicate damage to these organs.

TFV can reduce bone mineral density . Calcium or vitamin D supplements may be helpful. This is especially true for people with osteopenia or osteoporosis.

### Storage

Store at room temperature (15–30 °C). The shelf-life is 3 years but always check the label.

# 17

## NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIs)

**Class adverse drug reactions to non-nucleoside reverse transcriptase inhibitors (NNRTIs).**

### *Skin rash*

Skin rash occurs most commonly with the NNRTI class of drugs. Most cases are mild-to-moderate in nature, occurring within the first few weeks of therapy. Management of NNRTI-related skin rashes depends on the severity of the rash. In general, mild (grade 1) and moderate (grade 2) rashes can be managed with symptomatic therapy (antihistamines) and careful monitoring (daily visits or daily telephone progress reports). If patients experience severe or life-threatening skin reactions, the drugs need to be stopped immediately. More serious cutaneous manifestations such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis should result in the prompt and permanent discontinuation of the NNRTI or other offending agents.

Most cases of skin rash are confined to cutaneous reactions. However, a severe or even life-threatening syndrome of drug rash with eosinophilia and systemic symptoms has also been described. The systemic symptoms may include fever, haematological abnormalities and multiple organ involvement.

Among the NNRTIs, skin rash occurs more frequently and is greater in severity with NVP. Using a two-week lead-in dose escalation schedule when initiating NVP therapy may reduce the incidence of rash.

### *Acute symptomatic hepatitis*

Acute symptomatic hepatitis with jaundice, liver enlargement, gastrointestinal symptoms, fatigue and anorexia may occur. Hypersensitivity may manifest as rash, fever and other systemic symptoms, usually within 6–8 weeks of starting therapy. Lactic acidosis may occur. If adverse reactions occur, discontinue all ARVs until symptoms resolve. Transaminase and bilirubin levels should be monitored if possible. NVP should not be re-administered in the future but ART should be restarted using alternative ARVs.

## Efavirenz (EFV)

**Class:** Non-nucleoside reverse transcriptase inhibitor (NNRTI)

### Available formulations

- *Capsules:* 50 mg, 100 mg and 200 mg
- *Oral solution:* 30 mg/ml
- *Tablets:* 300 and 600 mg

### Uses

HIV infection in combination with at least two other ARV drugs in adults, adolescents and children.

### Contraindications

Contraindicated in patients with clinically significant hypersensitivity to EFV or any of the excipients (inactive ingredients) in the products.

EFV should not be administered concurrently with terfenadine, astemizole, cisapride, midazolam, triazolam, pimozone, bepridil or ergot derivatives because competition for CYP3A4 by EFV could result in inhibition of metabolism of these medicines and create the potential for serious and/or life-threatening adverse events (e.g. cardiac arrhythmias, prolonged sedation or respiratory depression).

EFV is contraindicated in the first trimester of pregnancy.

EFV must not be administered concurrently with voriconazole because EFV significantly decreases the plasma concentrations of voriconazole, while voriconazole significantly increases EFV plasma concentrations (see “Interactions”).

### Pregnancy

Pregnancy should be avoided in women treated with EFV. Barrier contraception should always be used in combination with other methods of contraception (e.g. oral or other hormonal contraceptives). Women of childbearing potential should undergo pregnancy testing before initiation of therapy with EFV. EFV should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the fetus and there are no other appropriate treatment options. If a woman takes EFV during the first trimester of pregnancy or becomes pregnant while taking EFV, she should be informed of the potential harm to the fetus.

## Breastfeeding

It is not known whether EFV is excreted in human milk. Since animal data suggest that the substance may be passed into breast milk, it is recommended that mothers taking EFV do not breastfeed their infants. It is recommended that HIV-infected women do not breastfeed their infants under any circumstances to avoid transmission of HIV.

## Precautions

EFV should be used with caution in patients with hepatic impairment, severe renal impairment, breastfeeding (*see* notes above), the elderly those with a history of mental illness or substance abuse.

*Rash:* Rash, usually in the first 2 weeks, is the most common adverse effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—rash usually resolves within 1 month.

*See also* “Class adverse drug reactions to non-nucleoside reverse transcriptase inhibitors (NNRTIs)”, p. 58.

## Dosage

*Adults:* 600 mg once daily

*Children* > 3 years of age and depending on weight—*see* table below

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

Weight	Paediatric dose
From 10 to < 15 kg	200 mg (caps) once daily 270 mg (= 9 ml oral solution) once daily
From 15 to < 20 kg	250 mg (caps) once daily 300 mg (= 10 ml oral solution) once daily
From 20 to < 25 kg	300 mg (caps) once daily 360 mg (= 12 ml oral solution) once daily
From 25 to < 33 kg	350 mg (caps) once daily 450 mg (= 15 ml oral solution) once daily
From 33 to < 40 kg	400 mg (caps) once daily or 510 mg (= 17 ml oral solution) once daily
> 40 kg	600 mg once daily

Capsules may be opened and added to food but have a very peppery taste; however, the contents can be mixed with sweet foods or jam to disguise the taste.

## Food effect

Can be taken with or without food; a high fat meal should be avoided.

## Metabolism

Mainly in the liver

## Interactions

It causes 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.

EFV levels are decreased by rifampicin and SQV. No dose adjustment in EFV (600 mg OD) is required when co-administered with rifampicin.

EFV increases the levels of NFV and RTV.

EFV decreases the levels of amprenavir (APV), clarithromycin; IDV; LPV; §methadone; rifabutin and SQV.

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

Methadone dose may need to be increased by up to 50% in 5–10 mg increments per day.

## Adverse effects

*Rash including SJS:* In clinical trials, 26% of patients treated with 600 mg of EFV experienced skin rash compared with 17% of patients treated in control groups. Skin rash was considered treatment-related in 18% of patients treated with EFV. Severe rash occurred in <1% of patients treated with EFV and 1.7% discontinued therapy because of rash. The incidence of erythema multiforme or SJS was 0.14% (*see also* “Class adverse drug reactions”, p. 58).

*Additional adverse effects:* Dizziness, headache, insomnia, somnolence, abnormal dreams, fatigue, impaired concentration can persist for up to three months. Many patients will adapt but some continue to find the CNS side-effects intolerable and EFV will need to be substituted with another ARV (administration at bedtime especially in the first 2–4 weeks reduces the CNS effects). Potentially more serious CNS side-effects are severe depression (2.4%), aggressive behaviour, paranoid reactions and manic reactions. Nausea; less frequently vomiting, diarrhoea, hepatitis (*see also* “Class adverse drug reactions”, p. 58), depression, anxiety, psychosis, amnesia, ataxia, stupor, vertigo; also reported raised serum

cholesterol, raised liver enzymes (especially if seropositive for hepatitis B or C), pancreatitis.

### Storage

*Capsules 200 and 600 mg:* Store at room temperature (15–30°C). The shelf-life is 2 years.

*Hard capsules:* 50 and 100 mg. Store at room temperature (15–30°C). The shelf-life is 3 years.

*Hard capsules 200 mg:* Store at room temperature (15–30°C). The shelf-life is 2 years for blister packs, 3 years for bottles.

*Oral solution:* 30 mg/ml. Store at room temperature (15–30°C). The shelf-life is 3 years. The oral solution should be used within one month of first opening the bottle.

*Tablets 300 and 600 mg:* Store at room temperature (15–30°C). The shelf-life is 2 years.



## Nevirapine (NVP)

**Class:** Non-nucleoside reverse transcriptase inhibitor (NNRTI)

### Available formulations

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

### Uses

HIV infection, in combination with at least two other ARV drugs; PMTCT in HIV-infected patients (*see notes under “Pregnancy”*).

### Contraindications

The first 18 weeks of therapy with NVP are a critical period during which close monitoring of patients is required to look for the potential appearance of severe and life-threatening skin reactions (including cases of SJS and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. The greatest risk of hepatic events and skin reactions occurs during the first 6 weeks of therapy. However, the risk of any hepatic event continues past this period and monitoring should continue at frequent intervals. Female gender and higher CD4 counts at initiation of therapy place patients at greater risk for hepatic adverse events. Unless the benefit outweighs the risk, NVP should not be started in adult females with CD4 cell counts  $>250$  cells/mm<sup>3</sup> or in adult males with CD4 cell counts  $>400$  cells/mm<sup>3</sup>. This is based on the occurrence of serious and life-threatening hepatotoxicity in controlled and uncontrolled studies.

In some cases, hepatic injury has progressed despite discontinuation of treatment. Patients developing signs or symptoms of hepatitis, severe skin reaction or hypersensitivity reactions must discontinue NVP and seek medical evaluation immediately. NVP should not be restarted following severe hepatic, skin or hypersensitivity reactions.

The dosage must be strictly adhered to, especially during the 14-day lead-in period.

NVP is contraindicated in patients with clinically significant hypersensitivity to NVP or any of the excipients (inactive ingredients) of the products.

NVP should not be administered to patients with severe hepatic dysfunction.

NVP should not be readministered to patients who have required discontinuation for severe rash, rash accompanied by constitutional symptoms, hypersensitivity reactions or clinical hepatitis due to NVP.

NVP should not be readministered to patients who previously had AST or ALT levels >5 times the upper limit of normal (ULN) during NVP therapy and had rapid recurrence of liver function abnormalities upon readministration of NVP.

### Pregnancy

NVP should be included in all ART regimens in pregnant women with CD4 counts <250 cells/mm<sup>3</sup> who need ART for their own health.

NVP for the PMTCT of HIV-1 has been demonstrated to be safe and effective when given as part of a regimen that includes a single 200 mg oral dose to mothers during labour followed by a single 2 mg/kg dose to the infant within 72 hours of birth.

High levels of NVP resistance (30–50%) have been reported in women following administration of a single dose of NVP for PMTCT.

### Breastfeeding

It is recommended that HIV-infected mothers not breastfeed their infants to avoid the risk of postnatal transmission of HIV.

### Precautions

Hepatic impairment, history of chronic hepatitis (greater risk of hepatic adverse effects), pregnancy and breastfeeding

*Hepatic disease:* Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported, usually occurring in first 8 weeks; if possible, monitor liver function before long-term treatment then every 2 weeks for 2 months, then after 1 month and then every 3–6 months; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction; discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild-to-moderate abnormalities in liver function tests with no hypersensitivity reaction.

Patients, particularly women, with increased CD4+ cell counts at initiation of NVP therapy (>250 cells/mm<sup>3</sup> in women and >400 cells/mm<sup>3</sup> in men) are at higher risk for the development of symptomatic hepatic events, often associated with rash. The risk of symptomatic hepatic events regardless of severity is greatest during the first 6 weeks of therapy. However, hepatic events may occur at any time during treatment. In some cases, patients

presented with non-specific, prodromal signs or symptoms of fatigue, malaise, anorexia, nausea, jaundice, liver tenderness or hepatomegaly, with or without initially abnormal serum transaminase levels. Patients who have infection with hepatitis B or C and/or altered liver function tests at the start of therapy with NVP are at greater risk of later symptomatic events (6 weeks or more after starting NVP) and asymptomatic increases in AST or ALT.

*Rash:* Rash, usually in first 8 weeks, is the most common adverse effect (*see also* “Class adverse drug reactions”, p. 58); incidence reduced if introduced at 200 mg od and increased to 200 mg twice daily after 2 weeks; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, swelling, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves.

## Dosage

*Adults:* 200 mg once daily for the first 14 days. If no rash is present, 200 mg (1 tablet) twice daily

*Children:* 15–30 days: 5 mg/kg/dose once daily  $\times$  2 weeks, then 120 mg/m<sup>2</sup>/dose twice daily  $\times$  2 weeks, then 200 mg/m<sup>2</sup>/dose twice daily

>30 days–13 years: 120 mg/m<sup>2</sup>/dose once daily for 2 weeks, then 120–200 mg/m<sup>2</sup>/dose twice daily

*Maximum dose:* >13 years: 200 mg/dose once daily for first 2 weeks, then 200 mg/dose twice daily

Tablets are scored and can be divided into two equal halves to give a 100 mg dose; can be crushed and combined with a small amount of water or food and immediately administered.

If treatment is interrupted for >7 days reintroduce with 200 mg daily (infant 15–30 days old, 5 mg/kg; child over 1 month, 120 mg/m<sup>2</sup>)<sup>21</sup> and increase dose cautiously.

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.

*PMTCT of HIV:* By mouth, adult 200 mg as a single dose at onset of labour; neonate 2 mg/kg as a single dose within 72 hours of birth.

<sup>21</sup> See Chapter 7 for calculation of body surface area

### Food effect

Can be taken with or without food

### Metabolism

Mainly in the liver

### Interactions

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*).

NVP levels are increased by cimetidine, clarithromycin and IDV.

NVP levels are decreased by rifampicin and rifabutin. In patients with HIV/TB co-infection and receiving rifampicin, an EFV-containing regimen is preferred. If EFV is unavailable, standard doses of NVP may be used with rifampicin but subtherapeutic NVP levels may occur in some patients. Dose increase in NVP is not recommended due to the risk of hepatotoxicity.

NVP decreases the levels of clarithromycin, IDV, LPV, methadone, RTV and SQV (to be given together only if co-administered with RTV);

Methadone dose may need to be increased when co-administered with NVP (*see* Chapter 12).

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

### Adverse effects

Rash including SJS and rarely toxic epidermal necrolysis (*see also* "Precautions" above); hepatitis or jaundice reported (*see also* "Precautions" above); nausea, vomiting, abdominal pain, diarrhoea, headache, drowsiness, fatigue, fever; hypersensitivity reactions (may involve hepatic reactions and rash, *see* "Precautions" above); anaphylaxis, angioedema, urticaria also reported.

### Storage

*Oral suspension 10 mg/ml:* Store at room temperature (15–30°C). The shelf-life is 2 years. Shelf-life after opening the bottle is 2 months only.

*Tablets 200 mg:* Store at room temperature (15–30°C). The shelf-life is 2 years.

# 18

## PROTEASE INHIBITORS (PIs)

### Class adverse drug reactions to protease inhibitors (PIs)

#### Hyperglycaemia

New-onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of existing diabetes mellitus, as well as hyperglycaemia, insulin resistance or glucose tolerance have all been reported in patients receiving PIs. Insulin resistance occurs in up to 40% of patients treated with PIs, while hyperglycaemia has been reported in 3–17% of patients receiving PIs (median onset is 60 days after initiation of therapy, ranging from 2 to 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 PI therapy and initiated treatment with oral hypoglycaemic 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 if suspect signs and symptoms such as polydipsia or polyuria occur 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, lipodystrophy syndrome, fat redistribution syndrome are frequently (13–84%) observed in patients treated with PIs. These changes have also been described with NsRTI 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.

Central fat accumulation appears to be more associated with PIs and peripheral fat wasting with NsRTIs. Hyperlipidaemia and insulin resistance are frequently, but not always, associated with lipodystrophy. Therapeutic strategies have included switching classes of ARVs and exercise training. Reversal of body

shape changes may not occur or may occur only slowly once the offending ARV agent has been discontinued. Specific drug treatments for this condition are being actively investigated.

### Hyperlipidaemia

Changes in blood levels of triglycerides and/or cholesterol have been observed very frequently, even in the absence of fat redistribution. Although all PIs have been implicated, RTV produces substantial increases in triglycerides and cholesterol most frequently, which reach higher blood levels than with other PIs.

The observed prolonged important increases in triglycerides and/or cholesterol are of concern because of the possible association with cardiovascular events and pancreatitis. 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 the 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 these as much as possible.

Intervention is usually recommended for triglyceride levels  $>750$ – $1000$  mg/dl and/or low-density lipoprotein (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 was found to be beneficial; but such a decision requires a careful risk–benefit analysis.

## Amprenavir (APV)

**Class:** Protease inhibitor (PI)

### Available formulations

- *Oral suspension:* 15 mg/ml
- *Capsules:* 150 mg

### Uses

For the treatment of HIV-infected patients in combination with other ARV agents

### Contraindications

Known hypersensitivity to APV or any ingredient product

There is a potential risk of toxicity from the excipient propylene glycol in oral solution. The ability to metabolize propylene glycol may not be fully developed in children < 4 years of age. Children < 4 years of age should not receive APV oral solution.

APV must not be administered concurrently with medicinal products with narrow therapeutic windows which are substrates of cytochrome P450 3A4 (CYP 3A4). Co-administration may result in competitive inhibition of the metabolism of these medicinal products and create the potential for serious and/or life-threatening adverse events such as cardiac arrhythmia (e.g. terfenadine, astemizole, cisapride, pimozone), prolonged sedation or respiratory depression (e.g. triazolam, midazolam) or peripheral vasospasm or ischaemia (e.g. ergot derivatives) (see “Interaction with other medicinal products and other forms of interaction”).

Rifampicin must not be administered concurrently with APV. Rifampicin decreases the APV plasma AUC by approximately 82%.

### Warning

Because of the potential risk of toxicity from the large amount of the excipient propylene glycol, APV oral solution is **contraindicated in infants and children < 4 years of age, pregnant women and patients with hepatic or renal failure**. Certain ethnic populations, such as Asians, Eskimos and Native Americans, may be at increased risk for propylene glycol-associated adverse events because of alcohol dehydrogenase polymorphisms; however, no data are available on propylene glycol metabolism in these groups.

### Pregnancy

APV oral solution should not be used during pregnancy due to the potential

risk of toxicity to the fetus from the propylene glycol content. If APV is used during pregnancy, the capsule form should be used. Placental transfer of APV and/or its related metabolites has been shown to occur in animals.

In pregnant rats and rabbits there were no major effects on embryo-fetal development. A number of minor changes, including thymic elongation and minor skeletal variations were seen, indicating developmental delay. Systemic plasma exposure (AUC) to APV in pregnant rabbits was significantly lower at all doses compared with plasma exposure found in patients in clinical studies.

Because animal reproduction studies are not always predictive of human response, this medicine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Breastfeeding

APV-related material was found in rat milk, but it is not known whether APV is excreted in human milk. A reproduction study in pregnant rats, dosed from the time of uterine implantation through lactation, showed reduced body weights in the offspring. It is therefore recommended that mothers being treated with APV do not breastfeed their infants. Additionally, it is recommended by health experts that, where possible, HIV-infected women do not breastfeed their infants in order to avoid transmission of HIV.

### Precautions

APV should be used with caution in patients with hepatic impairment. The dose of APV should be reduced in patients with moderate or severe hepatic impairment.

APV, like other PIs, is an inhibitor of the cytochrome P450 CYP3A4 enzyme. APV should not be administered concurrently with medications with narrow therapeutic windows which are substrates of CYP3A4. There are also other agents that may result in serious and/or life-threatening drug interactions; therefore, caution is advised whenever APV is co-administered with medicinal products that are inducers, inhibitors or substrates of CYP3A4 (*see* “Contraindications” and “Interactions with other drugs”).

Pharmacokinetic studies with other CYP3A4 inhibitors, including other PIs, indicate that APV may significantly increase lovastatin and simvastatin concentrations, which have been associated with an increased incidence of myopathy, including rhabdomyolysis. Co-administration with lovastatin or simvastatin is not recommended.

APV may increase atorvastatin concentrations. Use the lowest possible dose of atorvastatin with careful monitoring or consider the use of pravastatin or fluvastatin as alternative HMG-CoA reductase inhibitors in combination with APV.



Although the isozyme(s) responsible for bepridil metabolism has (have) not been elucidated, the metabolic pathways primarily responsible for bepridil metabolism are mediated by the CYP450 enzyme system. Because APV is an inhibitor of the CYP3A4 isozyme, the CYP450 isozyme most commonly responsible for drug metabolism, and because increased plasma bepridil exposure may increase the risk of life-threatening arrhythmia, caution is warranted when APV and bepridil are co-administered.

Serious and/or life-threatening drug interactions could occur between APV and amiodarone, lidocaine (systemic), tricyclic antidepressants, quinidine and warfarin. Concentration monitoring (warfarin—monitor international normalized ratio [INR]) of these agents is recommended as this should minimize the risk of potential safety problems with concomitant use.

Concomitant use of APV and products containing *Hypericum perforatum* (also known as St John's wort) is not recommended. A pharmacokinetic study with IDV indicates that *Hypericum perforatum* may reduce APV serum concentrations when administered concomitantly (see "Interactions with other drugs").

Because of the potential for metabolic interactions with APV, the efficacy of hormonal contraceptives may be modified, but there is insufficient information to predict the nature of the interactions. Therefore, alternative methods of contraception are recommended for women of childbearing potential.

There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in patients with haemophilia types A and B treated with PIs. In some patients, additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued, or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Patients with haemophilia should therefore be made aware of the possibility of increased bleeding.

Patients should be advised that APV, or any other current ARV, does not cure HIV infection; they may still develop opportunistic infections, and other complications of HIV infection. Current ARVs, including APV, have not been proven to prevent the risk of transmission of HIV to others through sexual contact or blood contamination. Appropriate precautions should continue to be taken.

## Dosage

*Adults and adolescents (≥ 13 years of age; > 50 kg body weight):* The recommended dose of APV capsules is 1200 mg twice daily in combination with other ARV agents.

If APV capsules are used in combination with RTV in adults, reduced doses of APV (600 mg twice daily) and RTV (100 mg twice daily) are recommended.

*Adults and adolescents ( $\geq 13$  years of age;  $> 50$  kg body weight) unable to swallow capsules:* The recommended dose of APV oral solution is 1400 mg (93.3 ml) twice daily in combination with other ARVs.

*Children (4–12 years) and subjects  $< 50$  kg body weight:* The recommended dose of APV capsules is 20 mg/kg body weight twice a day, or 15 mg/kg three times a day, in combination with other ARVs, without exceeding a total daily dose of 2400 mg.

The pharmacokinetic interactions between APV and low doses of RTV or other PIs have not yet been evaluated in children. Therefore, such combinations should be avoided in children.

*Children (4–12 years) and subjects  $< 50$  kg body weight unable to swallow capsules:* The recommended dose of APV oral solution is 22.5 mg (1.5 ml)/kg body weight twice a day, or 17 mg (1.1 ml)/kg three times a day, in combination with other ARV agents, without exceeding a total daily dose of 2800 mg.

*Children  $< 4$  years of age:* APV oral solution and capsules are contraindicated for use in children  $< 4$  years of age as safety and efficacy have not yet been established in this age group.

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

### Food effect

Can be taken with or without food; a high fat meal should be avoided.

### Metabolism

APV is primarily metabolized by the liver with  $< 3\%$  excreted unchanged in the urine. The primary route of metabolism is via the cytochrome P450 CYP3A4 enzyme. APV is a substrate of and inhibits CYP3A4. Therefore, medicines that are inducers, inhibitors or substrates of CYP3A4 must be used with caution when administered concurrently with APV.

### Warning

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 ddI 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, pimozone, rifampicin, St John's wort (*Hypericum perforatum*), simvastatin, terfenadine and triazolam.
- Because of the large amount of the excipient propylene glycol, APV oral solution should not be co-administered with disulfiram or metronidazole or some cephalosporins such as cefamandole or cefoperazone.
- APV levels are increased by ABC (§APV), delavirdine, clarithromycin, IDV, ketoconazole, §RTV and AZT (§APV).
- APV levels are decreased by dexamethasone, EFV (§APV), §LPV (§APV), NVP, rifampicin, §rifabutin and SQV.
- APV increases the levels of carbamazepine, clarithromycin, itraconazole, ketoconazole, NFV, rifabutin, sildenafil and AZT.
- APV decreases the levels of IDV, LPV (§APV) and SQV.
- Potential interactions with anticonvulsants, benzodiazepines, calcium-channel blockers, statins, oral contraceptives, tricyclic antidepressants, oral anticoagulants, amiodarone, methadone, quinidine and immunosuppressants.

## Adverse effects

Adverse events have been reported during treatment with APV. For many of these events it is unclear whether they are related to APV, or to concomitant treatment with the wide range of medicines used in the management of HIV disease, or a result of the disease process.

Most undesirable effects associated with APV therapy were mild-to-moderate in severity, early in onset, and rarely treatment-limiting. In children the emerging safety profile is similar in nature to that seen in adults.

From clinical studies, gastrointestinal events (nausea, diarrhoea, flatulence and vomiting) were the most commonly reported undesirable effects. There were also reports of oral/perioral paraesthesia, rash, headache and fatigue, which were considered to be related to treatment with APV.

Rash generally occurred during the second week of treatment and usually resolved spontaneously within two weeks, without stopping APV. However, occasionally the rash may be severe and cases of SJS have been reported rarely. Only 3% of patients discontinued APV due to a rash.

In clinical studies, reports of symptoms of abnormal fat redistribution (*see* “Class adverse drug reactions”, p. 67) were infrequent with APV (< 1% of ARV-naive patients and < 4% of NRTI-experienced patients).

Laboratory abnormalities occurred infrequently, and primarily in patients with abnormal values at baseline. Overall, the most frequently reported clinically significant laboratory abnormalities considered related to treatment with APV were raised levels of transaminases and triglycerides.

***See also* “Class adverse drug reactions to protease inhibitors” (hyperglycaemia and hyperlipidaemia), pp 67–68.**

### **Storage**

*Oral solution:* Store at room temperature (15–30°C). The shelf-life is 24 months.

*Capsules:* Store at room temperature (15–30°C). The shelf-life is 18 months.

## Atazanavir (ATZ)

**Class:** Protease inhibitor (PI)

### Available formulations

*Capsules:* 100, 150 and 200 mg. Each capsule contains 100, 150 and 200 mg of ATZ (corresponding respectively to 113.9, 170.85, and 227.8 mg ATZ sulfate).

### Uses

For the treatment of HIV-infected patients in combination with other ARV agents.

### Contraindications

These include known hypersensitivity to ATZ or any ingredient of the products; moderate hepatic dysfunction; co-administration of ATZ is contraindicated with drugs that are highly dependent on cytochrome P450 3A4 for clearance (such as midazolam, triazolam, dihydroergotamine, ergotamine, ergonovine, methylergonovine, cisapride and pimozide) and for which elevated plasma concentrations are associated with serious and/or life-threatening events.

ATZ should not be used in combination with rifampicin.

### Pregnancy

There are no adequate and well-controlled studies in pregnant women. Cases of lactic acidosis syndrome, sometimes fatal, and symptomatic hyperlactataemia have been reported in patients (including pregnant women) receiving ATZ in combination with nucleoside analogues, which are known to be associated with an increased risk of the lactic acidosis syndrome. ATZ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Breastfeeding

It is not known whether ATZ is secreted in human milk. A study in lactating rats has demonstrated that ATZ is secreted in milk. Because of the potential for both HIV transmission and for serious adverse reactions in nursing infants, mothers should be instructed not to breastfeed if they are receiving ATZ.

### Precautions

*Hyperbilirubinaemia:* Most patients taking ATZ experience asymptomatic increase in indirect (unconjugated) bilirubin related to inhibition of uridine diphosphoglucuronyl transferase. This hyperbilirubinaemia is reversible on

discontinuation of ATZ. The increase in levels of hepatic transaminases that occur with hyperbilirubinaemia should be evaluated for alternative causes. No long-term safety data are available for patients experiencing persistent rise in total bilirubin > 5 times ULN. An alternative ART to ATZ may be considered if jaundice or scleral icterus associated with raised bilirubin levels is of cosmetic concern for the patient.

Dose reduction of ATZ is not recommended since the long-term efficacy of reduced doses has not been established.

*Rash:* In controlled clinical trials (n=1597), rash (all grades, regardless of causality) occurred in 21% of patients treated with ATZ. The median time to onset of rash was 8 weeks after initiation of ATZ and the median duration of rash was 1.3 weeks. Rashes were generally mild-to-moderate maculopapular skin eruptions. Dosing with ATZ was often continued without interruption in patients who developed rash. The discontinuation rate due to rash in clinical trials was 0.4%. ATZ should be discontinued if severe rash develops. Cases of SJS and erythema multiforme have been reported in patients receiving ATZ.

*Hepatic impairment and toxicity:* ATZ is principally metabolized by the liver; caution should be exercised when administering this drug to patients with hepatic impairment because ATZ concentrations may be increased. Patients with underlying hepatitis B or C viral infections or marked increase in transaminases prior to treatment may be at increased risk for developing a further increase in transaminase levels or hepatic decompensation. There are no clinical trial data on the use of ATZ/r in patients with any degree of hepatic impairment.

## Dosage

*Therapy-naïve patients:* 400 mg (two 200 mg capsules) once daily taken with food.

*Therapy-experienced patients:* 300 mg (two 150 mg capsules) once daily plus RTV 100 mg once daily taken with food.

*Children:* Paediatric use is not approved. (The pharmacokinetics of ATZ in paediatric patients are under investigation. There are insufficient data at this time to recommend a dose.)

## Food effect

It is recommended to take ATZ with food. Administration with food enhances bioavailability and reduces pharmacokinetic variability. Administration of a single 400 mg dose of ATZ with a light meal results in a 70% increase in AUC and 57% increase in  $C_{max}$  relative to the fasting state.

## Metabolism

ATZ is extensively metabolized in the liver. The major biotransformation pathways of ATZ in humans consist of mono-oxygenation and dioxygenation. Other minor biotransformation pathways for ATZ or its metabolites consist of glucuronidation.

*N-dealkylation, hydrolysis and oxygenation with dehydrogenation:* Two minor metabolites of ATZ in plasma have been characterized. Neither metabolite demonstrated in vitro antiviral activity. In vitro studies using human liver microsomes suggested that ATZ is metabolized by CYP3A.

## Interactions

- Yes; inhibition of CYP3A4 (cytochrome P450 3A4 isoform). Co-administration of ATZ and drugs primarily metabolized by CYP3A (e.g. calcium-channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drug, which could increase or prolong its therapeutic and adverse effects.
- If ATZ is to be co-administered with EFV or TFV, it is recommended that ATZ is given at the dose of 300 mg with RTV 100 mg (all as a single daily dose with food), as this combination results in ATZ exposure that approximates the mean exposure to ATZ produced by 400 mg alone. **ATZ without RTV should not be co-administered with EFV or TFV.**
- Concomitant use of ATZ with lovastatin or simvastatin is not recommended due to the risk of myopathy, including rhabdomyolysis.
- Co-administration of ATZ with warfarin has the potential to produce serious and/or life-threatening bleeding and has not been studied.
- It is not recommended to co-administer ATZ with IDV, proton pump inhibitors, benzodiazepines such as midazolam and triazolam, ergot derivatives, sildenafil and cisapride.
- Concomitant use of ATZ and St John's wort (*Hypericum perforatum*), or products containing St John's wort, is not recommended. Co-administration of PIs, including ATZ, with St John's wort is expected to substantially decrease concentrations of the PI and may result in suboptimal levels of ATZ leading to loss of virological response and possible resistance to ATZ or to the class of PIs.
- When used in combination with ATZ, a dose reduction of diltiazem by one half should be considered and ECG monitoring is recommended.

## Adverse effects

The experience regarding the safety and tolerance of ATZ in combination with RTV is limited.

The following adverse effects have been observed in case of co-administration with other ARV medicines:

*Body as a whole:* Fever, headache

*Cardiovascular system:* Second-degree atrioventricular (AV) block

*Digestive system:* Jaundice/scleral icterus, diarrhoea, nausea, vomiting, abdominal pain

*Nervous system:* Dizziness, insomnia, peripheral neurological symptoms, depression

*Musculoskeletal system:* Myalgia

*Skin:* Rash

**See also “Class adverse drug reactions to PIs” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.**

## Storage

Store at room temperature (15–30 °C). The shelf-life is 2 years.



## Fosamprenavir (Fos-APV)

**Class:** Protease inhibitor (PI)

### Available formulations

- *Tablet:* 700 mg. Each film-coated tablet contains 700 mg of Fos-APV as fosamprenavir calcium (equivalent to approximately 600 mg of APV).
- *Oral suspension:* 50 mg/ml. Each ml of oral suspension contains 50 mg Fos-APV as fosamprenavir calcium (equivalent to approximately 43 mg APV).

### Uses

Fos-APV is indicated in combination with other ARV agents for the treatment of HIV infection in adults.

*Paediatric patients:* The pharmacokinetics of APV after administration of Fos-APV to paediatric patients are under investigation. There are insufficient data at this time to recommend a dose.

### Contraindications

Fos-APV is contraindicated in patients with previously demonstrated clinically significant hypersensitivity to any of the components of this product or to APV.

Co-administration is contraindicated of Fos-APV with drugs that are highly dependent on CYP3A4 for clearance and in which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs include ergot derivatives such as dihydroergotamine, ergonovine, ergotamine and methylergonovine; the GI motility agent cisapride; the neuroleptic pimozide; and sedatives/hypnotics such as midazolam and triazolam.

Fos-APV with RTV must not be co-administered with medicinal products that have narrow therapeutic windows and are highly dependent on CYP2D6 metabolism, e.g. flecainide and propafenone.

Rifampicin must not be administered concurrently with Fos-APV.

Herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking Fos-APV due to the risk of decreased plasma concentrations and reduced clinical effects of APV.

### Pregnancy

Administration of Fos-APV to pregnant rats and rabbits produced no major effects on embryo-fetal development; however, the incidence of abortion was

increased in rabbits that were administered Fos-APV. There are no adequate and well-controlled studies in pregnant women. Fos-APV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Breastfeeding

Although it is not known if APV is excreted in human milk, Fos-APV is secreted in the milk of lactating rats. Because of both the potential for HIV transmission and for serious adverse reactions in nursing infants, mothers should be instructed **not** to breastfeed if they are receiving Fos-APV.

### Precautions

*Sulfa allergy:* Fos-APV should be used with caution in patients with a known sulfonamide allergy as Fos-APV contains a sulfonamide moiety. The potential for cross-sensitivity between drugs in the sulfonamide class and Fos-APV is unknown. In a clinical study of Fos-APV used as the sole PI, rash occurred in 2 of 10 patients (20%) with a history of sulfonamide allergy compared with 42 of 126 patients (33%) with no history of sulfonamide allergy. In 2 clinical studies of Fos-APV plus low-dose RTV, rash occurred in 8 of 50 patients (16%) with a history of sulfonamide allergy compared with 50 of 412 patients (12%) with no history of sulfonamide allergy.

*Hepatic impairment and toxicity:* Fos-APV is principally metabolized by the liver; therefore, caution should be exercised when administering Fos-APV to patients with hepatic impairment because APV concentrations may be increased. Patients with impaired hepatic function receiving Fos-APV without concurrent RTV may require dose reduction. There are no data on the use of Fos-APV in combination with RTV in patients with any degree of hepatic impairment. Patients with underlying hepatitis B or C or marked increase in transaminase levels prior to treatment may be at greater risk for developing further increase in transaminase levels. Appropriate laboratory testing should be conducted before initiating therapy with Fos-APV and patients should be monitored closely during treatment. Use of Fos-APV with RTV at higher-than-recommended dosages may result in raised transaminase levels and should not be used.

*Patients with haemophilia:* There have been reports of spontaneous bleeding in patients with haemophilia A and B treated with PIs. In some patients, additional factor VIII was required. In many of the reported cases, treatment with PIs was continued or restarted. A causal relationship between PI therapy and these episodes has not been established.

*Immune reconstitution inflammatory syndrome (IRIS):* IRIS has been reported in patients treated with ART, including Fos-APV. During the initial phase

of antiretroviral therapy (ART), patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jiroveci* pneumonia [PCP], or tuberculosis [TB]), which may necessitate further evaluation and treatment.

## Dosage

*Adults:* Two 700 mg tablets twice a day

or

One 700 mg tablet with 100 mg of RTV twice daily

or

Two 700 mg tablets with 200 mg of RTV once daily

*Children:* Paediatric use is not approved.

Twice daily RTV-boosted dosing is recommended for patients with known PI resistance.

## Food effect

Can be taken with or without food; a high fat meal should be avoided.

## Metabolism

APV is metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme system. The two major metabolites result from oxidation of the tetrahydrofuran and aniline moieties. Glucuronide conjugates of oxidized metabolites have been identified as minor metabolites in the urine and feces.

## Interactions

- Yes; inhibition of CYP3A4 (cytochrome P450 3A4 isoform).
- If ddI 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. (see also "Contraindications").
- Because of the large amount of the excipient propylene glycol, APV oral solution should not be co-administered with disulfiram or metronidazole or some cephalosporins, such as cefamandole or cefoperazone.

- Fos-APV levels are increased by ABC (SAPV), delavirdine, clarithromycin, IDV, ketoconazole, LPV, NFV, RTV (SAPV) and AZT.
- Fos-APV levels are decreased by dexamethasone, EFV (SAPV), LPV (SAPV), NFV, NVP, rifampicin, rifabutin and SQV.
- Fos-APV increases the levels of carbamazepine, clarithromycin, itraconazole, ketoconazole, rifabutin, sildenafil and AZT.
- Fos-APV decreases the levels of IDV, LPV (SAPV) and SQV.
- Potential interactions with anticonvulsants, benzodiazepines, calcium-channel blockers, statins, oral contraceptives, tricyclic antidepressants, oral anticoagulants, amiodarone, methadone, quinidine and immunosuppressants.

### Adverse effects

Fos-APV was studied in 700 patients in Phase III controlled clinical studies. The most common treatment-emergent adverse events in clinical studies of Fos-APV were diarrhoea, nausea, vomiting, headache and rash, which were generally mild-to-moderate in severity. Treatment discontinuation due to adverse events occurred in 6.4% of patients receiving Fos-APV and in 5.9% of patients receiving comparator treatments. Severe or life-threatening skin reactions, including one case of SJS among the 700 patients treated with Fos-APV, were reported and led to discontinuation of Fos-APV in < 1% of patients. Treatment with Fos-APV should be discontinued if the patient develops severe or life-threatening rashes or moderate rashes accompanied by systemic symptoms. Skin rash (without regard to causality) occurred in approximately 19% of patients treated with Fos-APV in the pivotal efficacy studies. Rashes were usually maculopapular and of mild or moderate intensity, some with pruritus. Rash had a median onset of 11 days after initiation of Fos-APV and a median duration of 13 days. In some patients with mild or moderate rash, dosing with Fos-APV was continued without interruption; if interrupted, reintroduction of Fos-APV generally did not result in recurrence of rash.

See also “Class adverse drug reactions to protease inhibitors” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.

### Storage

- *Tablet*: 700 mg; Room temperature (15–30°C). Shelf-life: 3 years
- *Oral suspension* 50 mg/ml: Store at 2–30°C; do not freeze. The shelf-life is 2 years. Discard 28 days after first opening.

## Indinavir (IDV)

**Class:** Protease inhibitor (PI)

### Available formulations

*Capsules:* 100, 200, 333 and 400 mg. Each hard capsule contains 125 mg of indinavir sulphate corresponding to 100 mg of IDV.

### Uses

IDV is indicated in combination with ARV nucleoside analogues for the treatment of HIV-1 infected adults, adolescents and children 4 years of age and older. In adolescents and children, the benefit of IDV therapy versus the increased risk of nephrolithiasis should be particularly considered.

### Contraindications

IDV is contraindicated in patients with clinically significant hypersensitivity to any of its components. IDV should not be administered concurrently with terfenadine, cisapride, astemizole, triazolam, midazolam, pimozone or ergot derivatives. Inhibition of CYP3A4 by IDV could result in raised plasma concentrations of these medicines, causing potentially serious or life-threatening reactions.

### Pregnancy

There are no adequate and well-controlled studies in pregnant patients. Increased frequency of gestational diabetes has been reported in pregnant women receiving IDV. IDV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Given that substantially lower antepartum exposures have been observed in a small study of HIV-infected pregnant patients and the limited data in this patient population, IDV use is not recommended in HIV-infected pregnant patients.

In rhesus monkeys administration of IDV to neonates caused a mild exacerbation of the transient physiological hyperbilirubinaemia seen in this species after birth. Administration of IDV to pregnant rhesus monkeys during the third trimester did not cause a similar exacerbation in neonates; however, only limited placental transfer of IDV occurred.

Hyperbilirubinaemia has occurred in both healthy subjects and HIV-1 infected patients treated with various dosage levels of IDV and has rarely been associated with increases in serum transaminases. However, because of the theoretical potential for the compound to exacerbate the physiological hyperbilirubinaemia seen in human neonates, careful consideration must be given to the use of IDV in pregnant women at the time of delivery.

## Breastfeeding

It is not known whether IDV is excreted in human milk. Because many medicines are excreted in human milk, and because of the potential for adverse reactions from IDV in nursing infants, mothers should be instructed to discontinue nursing if they are receiving IDV.

## Precautions

Nephrolithiasis has occurred with IDV therapy in adult and paediatric patients. The frequency of nephrolithiasis is higher in paediatric than in adult patients. In some cases, nephrolithiasis has been associated with renal insufficiency or acute renal failure; in the majority of these cases renal insufficiency and acute renal failure were reversible. If signs and symptoms of nephrolithiasis, including flank pain with or without haematuria (including microscopic haematuria) occur, temporary interruption of therapy (e.g. for 1–3 days) during the acute episode of nephrolithiasis or discontinuation of therapy may be considered. Paediatric patients who experience flank pain should be evaluated for the possibility of nephrolithiasis. Evaluation may consist of urinalysis, serum blood urea nitrogen and creatinine, and ultrasound of the bladder and kidneys. The long-term effects of nephrolithiasis in paediatric patients are unknown. Adequate hydration is recommended in all patients on IDV.

Cases of interstitial nephritis with medullary calcification and cortical atrophy have been observed in patients with asymptomatic severe leucocyturia (>100 cells/high power field). In patients at increased risk such as children, urinary screening should be considered. If persistent severe leucocyturia is found, further investigation might be warranted.

## Dosage

*Adults:* The recommended dosage of IDV is 800 mg orally every 8 hours.

*Children and adolescents (4–17 years of age):* The recommended dosage of IDV for patients 4–17 years of age is 500 mg/m<sup>2</sup> (dose adjusted from calculated body surface area<sup>22</sup> based on height and weight) orally every 8 hours. This dose should not exceed the equivalent of the adult dose of 800 mg every 8 hours.

IDV hard capsules should only be given to children who are able to swallow hard capsules.

IDV use has not been studied in children <4 years of age.

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<sup>22</sup> See Chapter 7 for calculation of body surface area.

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

### Food effect

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

### Metabolism

Mainly in the liver; <20% is eliminated unchanged in the urine.

### Interactions

- Yes; inhibition of CYP3A4 (cytochrome P450 3A4 isoform).
- If ddI or antacids 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, pimozone, rifampicin, SQV (in vitro antagonism), simvastatin, St John's wort (*Hypericum perforatum*), terfenadine and triazolam.
- IDV levels are increased by clarithromycin, delavirdine (§IDV), ketoconazole (§IDV), itraconazole (§IDV), LPV/r (§IDV), NFV, quinidine, RTV (§IDV) and sildenafil.
- IDV levels are decreased by APV, EFV, (§IDV), fluconazole, grapefruit juice, NVP (§IDV), rifampicin and rifabutin (§IDV).
- Indinavir increases the levels of APV, clarithromycin, ethinyl estradiol, isoniazid, ketoconazole, NFV, NVP, rifabutin (§IDV), sildenafil, trimethoprim and AZT.
- IDV decreases the 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.

### Adverse effects

Nausea, vomiting, diarrhoea, abdominal discomfort, dyspepsia, flatulence, pancreatitis, dry mouth, taste disturbances; headache, dizziness, insomnia; myalgia, myositis, rhabdomyolysis, asthenia, hypoesthesia, paraesthesia;

hyperglycaemia; anaphylactoid reactions, rash (including SJS), pruritus, dry skin, hyperpigmentation, alopecia, paronychia; interstitial nephritis, nephrolithiasis (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children); hepatitis, transient hyperbilirubinaemia; blood disorders including neutropenia, haemolytic anaemia; lipodystrophy and metabolic effects (see notes above).

*See also* “Class adverse drug reactions to protease inhibitors” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.

### **Storage**

Store at room temperature (15–30°C). The shelf-life is 2–3 years (see the product labelling).



## Lopinavir with ritonavir (LPV/r)

**Class:** Protease inhibitor (PI)

### Available formulations

- *Oral suspension:* 80 mg/ml LPV + 20 mg/ml RTV (contains 42% alcohol)
- *Capsules:* 133/33r mg (133.3 mg of LPV + 33.3 mg RTV)
- *Tablets (heat-stable formulation):* 200 mg LPV + 50 mg RTV

### Uses

LPV/r is indicated for the treatment of HIV-1 infected adults and children above the age of 6 months, in combination with other ARVs.

### Contraindications

LPV/r is contraindicated in patients with known hypersensitivity to LPV, RTV or any of the excipients (inactive ingredients) and in patients with severe hepatic insufficiency.

LPV/r contains LPV and RTV, both of which are inhibitors of the P450 isoform CYP3A.

### Pregnancy

There are no data on the use of LPV/r in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. LPV/r should not be used during pregnancy unless clearly necessary.

### Breastfeeding

Studies in rats revealed that LPV is excreted in the milk. It is not known whether this medicinal product is excreted in human milk. HIV-infected women must not breastfeed their infants under any circumstances to avoid transmission of HIV.

### Precautions

Hepatic impairment—avoid if severe; renal impairment; haemophilia; pregnancy; breastfeeding (*see notes above*); diabetes mellitus; oral solution contains propylene glycol—avoid in hepatic and renal impairment, and in pregnancy; increased susceptibility to propylene glycol toxicity in slow metabolizers (*see also* “Interactions” below).

### Dosage

*Children:*

>6 months to 13 years: 225 mg/m<sup>2</sup> LPV/57.5 mg/m<sup>2</sup> RTV twice daily<sup>23</sup> or weight-based dosing:

<sup>23</sup> *See Chapter 7 for calculation of body surface area.*

7–15 kg: 12 mg/kg LPV/3 mg/kg RTV/dose twice daily

15–40 kg: 10 mg/kg LPV/5 mg/kg RTV twice daily

*Maximum dose:* >40 kg: 400 mg LPV/100 mg RTV (3 capsules or 5 ml) twice daily

The dose should be administered using a calibrated oral dosing syringe.

The oral solution is the recommended option for the most accurate dosing in children based on body surface area. However, if it is judged necessary to resort to soft capsules in children, they should be used with particular caution since they are associated with less precise dosing capabilities. Therefore, children receiving soft capsules might have higher exposure (with the risk of increased toxicity) or suboptimal exposure (with the risk of insufficient efficacy). Consequently, when dosing children with soft capsules, therapeutic drug monitoring may be a useful tool to ensure appropriate LPV exposure in an individual patient.

**Children should switch from LPV/r oral solution to soft capsules as soon as they are able to swallow the capsule formulation.**

Capsules should *not* be crushed or opened, but must be swallowed whole.

#### *Adult and adolescent use*

*Capsules:* The recommended dosage of LPV/r is three capsules twice daily (400/100 mg twice daily) taken with food, or four capsules twice daily when combined with EFV or NVP (533/133.33 mg twice daily). Oral solution is available for patients who have difficulty swallowing.

#### *Tablets:*

Treatment-naïve patients: Two tablets twice daily irrespective of co-administration with EFV or NVP (400/100 mg twice daily)

Treatment-experienced patients: Three tablets twice daily when combined with EFV or NVP (600/150 mg twice daily).

### **Food effect**

Should be taken with food.

### **Metabolism**

Mainly in the liver. In vitro experiments with human hepatic microsomes indicate that LPV primarily undergoes oxidative metabolism. LPV is

extensively metabolized by the hepatic cytochrome P450 system, almost exclusively by isozyme CYP3A. RTV is a potent CYP3A inhibitor which inhibits the metabolism of LPV and therefore increases the plasma levels of LPV.

## Interactions

- Yes; inhibition of CYP3A4 and to a lesser extent of CYP2D6 (cytochrome P450 isoforms).
- If ddI or antacids are administered, they should be taken at least one hour apart.
- Contraindicated drugs (LPV not to be taken with these drugs): amiodarone, astemizole, cisapride, ergotamine and similar alkaloids, flecainide, garlic supplements, lovastatin, midazolam, pimozide, propafenone, rifampicin, simvastatin, St John's wort (*Hypericum perforatum*), terfenadine and triazolam.
- Rifampicin should not be used in combination with LPV/r because co-administration may cause large decreases in LPV concentrations which may in turn significantly decrease the therapeutic effect of LPV.
- LPV levels are increased by delavirdine and RTV.
- LPV levels are decreased by APV (§LPV), carbamazepine, dexamethasone, EFV (§LPV), ketoconazole, NVP (§LPV), phenobarbital; herbal preparations containing St John's wort (*Hypericum perforatum*) must not be used while taking LPV and RTV due to the risk of decreased plasma concentrations and reduced clinical effects of LPV and RTV; phenytoin, rifampicin and TFV.
- LPV increases the levels of amiodarone, APV, atorvastatin, bepridil, calcium-channel blockers, clarithromycin, ketoconazole, IDV, itraconazole, lidocaine (systemic), quinidine, rifabutin, SQV, sildenafil and tenofovir.
- LPV decreases the levels of APV (§LPV), atovaquone and methadone (see Chapter 12).
- 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.

## Adverse effects

Diarrhoea, nausea, vomiting, colitis, abdominal discomfort, asthenia, headache, insomnia; rash; less frequently, dry mouth, hepatic dysfunction, pancreatitis, dyspepsia, dysphagia, oesophagitis, influenza-like syndrome, appetite changes; hypertension, palpitations, thrombophlebitis, vasculitis, chest pain, dyspnoea, agitation, anxiety, ataxia, hypertonia, confusion, depression, dizziness, dyskinesia, paraesthesia, peripheral neuritis, somnolence; Cushing syndrome, hypothyroidism, sexual dysfunction, anaemia, leukopenia, dehydration, oedema, lactic acidosis; arthralgia, myalgia, abnormal vision, otitis media, taste disturbances, tinnitus; acne, alopecia, dry skin, pruritus, skin discoloration, nail disorders, sweating; lipodystrophy and metabolic effects (*see notes above*); raised bilirubin and lowered sodium, low platelet and low neutrophil counts also reported in children.

*See also* “Class adverse drug reactions to protease inhibitors” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.

## Storage

*Oral suspension:* 80 mg/ml LPV + 20 mg/ml RTV

Store oral suspension at 2–8°C (refrigerator) until dispensed. Avoid exposure to excessive heat. If stored at room temperature up to 25°C, use suspension within 2 months.

Shelf-life when stored in a refrigerator is 2 years.

*Capsules:* 133/33r mg (133.3 mg of LPV + 33.3 mg RTV)

Store capsules at 2–8°C (refrigerator) until dispensed. Avoid exposure to excessive heat. If stored at room temperature up to 25°C, use capsules within 2 months. Shelf-life when stored in a refrigerator is 2 years.

*Tablets:* 200/50 mg (200 mg of LPV + 50 mg RTV)

Store at room temperature (below 30°C). The shelf-life is 2 years.

## Nelfinavir (NFV)

**Class:** Protease inhibitor (PI)

### Available formulations

- *Powder for oral suspension (mix with liquid):* 200 mg per level teaspoon (50 mg per 1.25 ml scoop); 5 ml
- *Tablets:* 250 mg contains 292.25 mg of NFV mesilate corresponding to 250 mg of NFV (as free base).

### Uses

As a part of ART for HIV-1 infected adults, adolescents and children  $\geq 3$  years of age.

### Contraindications

Hypersensitivity to the active substance or to any of the excipients (inactive ingredients)

### Pregnancy

No treatment-related adverse effects were seen in animal reproductive toxicity studies in rats at doses providing systemic exposure comparable to that observed with the clinical dose. Clinical experience in pregnant women is limited. NFV should be given during pregnancy only if the expected benefit justifies the possible risk to the fetus.

### Breastfeeding

It is recommended that HIV-infected women do not breastfeed their infants under any circumstances to avoid transmission of HIV. Studies in lactating rats showed that NFV is excreted in breast milk. No data are available on NFV excretion in human breast milk. Mothers must be instructed to discontinue breastfeeding if they are receiving NFV.

### Precautions

*Liver disease:* The safety and efficacy of NFV has not been established in patients with significant underlying liver disorders. Patients with chronic hepatitis B or C and treated with ART are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these drugs. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during ART and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

*Renal impairment:* NFV should be administered with caution in patients with impaired renal function.

*Diabetes mellitus:* New-onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients receiving PIs. In some of these the hyperglycaemia was severe and in some cases also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes or hyperglycaemia.

*Haemophilia:* There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in patients with haemophilia types A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Patients with haemophilia should therefore be made aware of the possibility of increased bleeding.

## Dosage

*Adults:* 1250 mg (5 tablets) twice daily

*Children:* 30 mg/kg three times daily (*see table below for dosage*)

Age	Dose
< 1 year	50 mg/kg/dose three times daily or
	75 mg/kg/dose twice daily
> 1 and < 13 years	55–65 mg/kg/dose twice daily
≥ 13 years	Maximum dose 1250 mg/dose twice daily

## Food effect

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

## Metabolism

Mainly in the liver

## Interactions

- Yes; at CYP3A4 level (cytochrome P450 3A4 isoform).
- If ddI or antacids 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.

- NFV levels are increased by delavirdine, EFV, IDV, ketoconazole, RTV and SQV.
- NFV levels are decreased by rifampicin and rifabutin (§NFV).
- NFV increases the levels of APV, IDV, 3TC, rifabutin (§NFV), SQV and sildenafil.
- NFV decreases the levels of delavirdine, §methadone and AZT.
- Potential interactions with anticonvulsants, tricyclic antidepressants, immunosuppressants, oral contraceptives, statins and oral anticoagulants.

### Adverse effects

The safety of NFV 750 mg tid and 1250 mg bid was studied in 5000 patients who received the medicine either alone or in combination with nucleoside analogues. The majority of adverse events were of mild intensity. The most frequently reported adverse event among patients receiving NFV at the recommended doses was diarrhoea. In pivotal clinical trials, diarrhoea was rarely a cause for discontinuation of NFV and can often be easily managed with non-prescription anti-diarrhoeal agents.

*Other adverse effects:* Nausea, vomiting, flatulence, abdominal pain; rash; reports of raised creatine kinase, hepatitis, pancreatitis, neutropenia, hypersensitivity reactions including bronchospasm, fever, pruritus and facial oedema, lipodystrophy and metabolic effects (*see notes above*).

*See also* “Class adverse drug reactions to protease inhibitors” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.

### Storage

*Oral powder:* Store at room temperature (15–30°C). The shelf-life is 2–3 years depending on the manufacturer.

*Tablets:* Store at room temperature (15–30°C). The shelf-life is 2 years.

## Ritonavir (RTV, r)

**Class:** Protease inhibitor (PI)

### Available formulations

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

### Uses

RTV is indicated in combination with other ARVs for the treatment of HIV-1 infected patients (adults and children  $\geq 2$  years of age). In PI-experienced patients the choice of RTV should be based on individual viral resistance testing and treatment history of patients.

### Contraindications

RTV is contraindicated in patients with known hypersensitivity to RTV or any of its excipients (inactive ingredients) and in patients with severe hepatic impairment.

Based primarily on literature review, RTV is expected to produce large increases in the plasma concentrations of the following medicines: amiodarone, astemizole, bepridil, bupropion, cisapride, clozapine, dihydroergotamine, encainide, ergotamine, flecainide, meperidine, pimozone, piroxicam, propafenone, propoxyphene, quinidine and terfenadine. These agents have recognized risks of arrhythmias, haematological abnormalities, seizures, or other potentially serious adverse effects. Additionally, acute ergot toxicity characterized by peripheral vasospasm and ischaemia has been associated with co-administration of RTV and ergotamine or dihydroergotamine. These medicines should not be co-administered with RTV. In addition, RTV is likely to produce large increases in these highly metabolized sedatives and hypnotics: clorazepate, diazepam, estazolam, flurazepam, midazolam and triazolam. Due to the potential for extreme sedation and respiratory depression from these agents, they should not be co-administered with RTV. Concomitant use of RTV and rifabutin is contraindicated because of clinical consequences such as uveitis resulting from a multifold increase of rifabutin serum concentrations.

### Pregnancy

There are no studies in pregnant women. This medicine should be used during pregnancy only if the potential benefit clearly outweighs the potential risk.

### Breastfeeding

It is not known whether RTV is excreted in human milk. Milk excretion has not been measured in animal studies; however, a study in rats showed some effects on offspring development during lactation, which are compatible with



excretion of RTV in milk in that species. HIV-infected women should not breastfeed their infants under any circumstances to avoid transmission of HIV.

## Precautions

*Renal disease:* There are no data on the pharmacokinetics and safety of RTV in patients with significant renal dysfunction.

*Liver disease:* The safety and efficacy of RTV has not been established in patients with significant underlying liver disorders. RTV is contraindicated in patients with severe hepatic impairment. Patients with chronic hepatitis B or C and treated with ART are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer to the relevant product information for these drugs. Patients with pre-existing liver dysfunction including chronic active hepatitis have an increased frequency of liver function abnormalities during ART and should be monitored according to standard practice. If there is evidence of worsening liver disease in such patients, interruption or discontinuation of treatment must be considered.

*Haemophilia:* There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in patients with haemophilia types A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Patients with haemophilia should therefore be made aware of the possibility of increased bleeding.

## Dosage

*Oral solution:* 80 mg/ml

*Adults:* The recommended dosage of RTV solution is 600 mg (7.5 ml) twice daily by mouth. However, RTV is almost never used at full dose because of side-effects. The main uses of RTV are in boosting other PIs (100 mg bid) and in patients with HIV/TB co-infection who need a PI-based regimen (SQV/RTV 400mg/400mg plus NRTI backbone drugs).

*Single PI-containing combination regimen for adults:* Treatment should be initiated at 300 mg (3.75 ml) twice daily for a period of three days and increased by 100 mg (1.25 ml) in twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should not remain on 300 mg twice daily for more than 3 days.

*Dual PI-containing combination regimens:* Clinical experience with dual therapy including therapeutic doses of RTV with another PI is limited. RTV extensively inhibits the metabolism of most available PIs. Hence, any consideration of dual

therapy with RTV should take into account the pharmacokinetic interaction and safety data of involved agents. There is extensive cross-resistance in this class of agents. The combination of two PIs with the least overlapping patterns of resistance should be considered. The use of RTV in such regimens should be guided by these factors.

*RTV as a pharmacokinetic enhancer for other PIs:* In clinical practice RTV is frequently used as a pharmacokinetic enhancer (at low doses of 100–200 mg once or twice daily) to boost the plasma concentrations of other PIs in HIV-infected adult patients.

When RTV is used with SQV a cautious titration of the dose has been used by initiating RTV at a dose of 300 mg twice daily.

When RTV is used with IDV a cautious titration of the dose has been used by initiating RTV at a dose of 200 mg twice daily, increasing by 100 mg twice daily and reaching 400 mg twice daily within 2 weeks.

*Children ( $\geq 2$  years of age):* Not used on its own

*Capsules:* 100 mg

*Adults:* The recommended dosage of RTV soft capsules is 600 mg (6 capsules) twice daily. Gradually increasing the dose of RTV when initiating therapy may help to improve tolerance.

*Single PI-containing combination regimen for adults:* Treatment should be initiated at 300 mg (3 capsules) twice daily for a period of three days and increased by 100 mg (1 capsule) in twice daily increments up to 600 mg twice daily over a period of no longer than 14 days. Patients should not remain on 300 mg twice daily for more than 3 days.

*Dual PI-containing combination regimens:* Clinical experience with dual therapy including therapeutic doses of RTV with another PI is limited. RTV extensively inhibits the metabolism of most available PIs. Hence, any consideration of dual therapy with RTV should take into account the pharmacokinetic interaction and safety data of involved agents. There is extensive cross-resistance in this class of agents. The combination of two PIs with the least overlapping patterns of resistance should be considered. The use of RTV in such regimens should be guided by these factors.

*RTV as a pharmacokinetic enhancer for other PIs:* In clinical practice RTV is frequently used as a pharmacokinetic enhancer (at low doses of 100–200 mg once or twice daily) to boost the plasma concentrations of other PIs in HIV-infected adult patients.

When RTV is used with SQV a cautious titration of the dose has been used by initiating RTV at a dose of 300 mg twice daily.

## Food effect

Should be taken with food

## Metabolism

Mainly in the liver

## Interactions (see also contraindications)

- RTV strongly inhibits CYP3A4 and other CYP isoforms (cytochrome P450 isoforms).
- If dDI or antacids 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.
- RTV formulations contain alcohol, which can produce reactions when co-administered with disulfiram and other drugs that can produce similar reactions, such as metronidazole, cefamandole and cefoperazone.
- RTV levels are increased by clarithromycin, delavirdine, EFV, fluconazole and ketoconazole.
- RTV levels are decreased by NVP, rifampicin and TFV.
- RTV increases the levels of APV (§RTV), clarithromycin, desipramine, EFV, IDV (§RTV), ketoconazole, LPV, NFV, rifabutin, SQV (§RTV), sildenafil and trimethoprim.
- RTV decreases the levels of alprazolam, atovaquone, divaproex, ethinyl estradiol, lamotrigine, meperidine, methadone, phenytoin, sulfamethoxazole, theophylline, warfarin and AZT.
- Potential interactions with analgesics, anticonvulsants, statins, oral contraceptives, tricyclic antidepressants, oral anticoagulants, immunosuppressants, calcium-channel blockers, sedatives/hypnotics and methamphetamine.
- Oral solution contains 42% alcohol.

## Adverse effects

In clinical studies (Phase II/III), the following adverse events with possible, probable or unknown relationship to RTV have been reported in  $\geq 2\%$  of 1033 patients.

*Classification of expected frequencies:* Very common ( $> 1/10$ ); Common ( $> 1/100$ ,  $< 1/10$ ); Uncommon ( $> 1/1000$ ,  $< 1/100$ ); Rare ( $> 1/10,000$ ,  $< 1/1000$ ).

Nausea, diarrhoea, vomiting, asthenia, altered taste, circumoral and peripheral paraesthesia were very common and are felt to be clearly related to RTV.

*Nervous system disorders:* Dizziness, paraesthesia, hyperaesthesia, somnolence, insomnia and anxiety were commonly reported.

*Cardiovascular disorders:* Vasodilatation was commonly reported.

*Respiratory system disorders:* Pharyngitis and increased cough were commonly reported.

*Gastrointestinal disorders:* Abdominal pain was very commonly reported. Dyspepsia, anorexia, local throat irritation, flatulence, dry mouth, eructation and mouth ulcer were commonly reported.

*Musculoskeletal system disorders:* Increased CPK and myalgia were commonly reported. Myositis was rarely reported. Rarely, rhabdomyolysis has been reported with PIs, particularly in combination with nucleoside analogues.

*Skin and subcutaneous tissue disorders:* Rash, pruritus and sweating were commonly reported.

Allergic reactions including urticaria, mild skin eruptions, bronchospasm and angioedema have been reported. Rare cases of anaphylaxis and SJS have been reported.

*Other disorders:* Headache was very commonly reported. Fever, pain and weight loss were commonly reported.

There have been spontaneous reports of thrombocytopenia, seizure and menorrhagia. Dehydration usually associated with gastrointestinal symptoms, and sometimes resulting in hypotension, syncope, or renal insufficiency, has been reported. Syncope, orthostatic hypotension and renal insufficiency have also been reported without known dehydration.

See also “Class adverse drug reactions to protease inhibitors” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.

## Storage

*Capsules:* Should be stored in a refrigerator (2–8°C) until they are dispensed to the patient. Refrigeration by the patient is not required if used within 30 days and stored below 25°C. The shelf-life is 2 years.

*Oral solution:* Should be stored at room temperature (15–30°C). Do not refrigerate or freeze. Shake well before each use. If, after shaking, particles or precipitate can be seen in the solution, the patient should take the next dose and see their doctor about a fresh supply. The shelf-life is 6 months.

## Saquinavir (SQV)

**Class:** Protease inhibitor (PI)

### Available formulations

*Hard capsules:* 200 mg of SQV as saquinavir mesilate

*Tablets:* 500 mg as saquinavir mesilate

*Soft capsules:* 200 mg as the free base

### Uses

SQV is indicated for the treatment of HIV-1 infected adult patients. SQV should only be given in combination with RTV and other ARV medicinal products.

**Hard capsules and soft capsules are not bioequivalent and cannot be used interchangeably.** (However, with RTV boosting it makes no difference and they are interchangeable).

**Hard capsules may be used only if SQV is combined with RTV, which significantly inhibits the metabolism of SQV, to provide plasma SQV levels at least equal to those achieved with soft capsules.**

**When using SQV as the sole PI in an antiviral regimen, soft capsules is the recommended formulation.**

### Contraindications

SQV/r is contraindicated in patients with hypersensitivity to SQV, RTV or any of the excipients (inactive ingredients) contained in the capsule(s).

SQV/r should not be given together with other medicinal products which may interact and result in potentially life-threatening side-effects. Medicinal products which should not be given with SQV/r include terfenadine, astemizole, pimozide, cisapride, amiodarone, propafenone and flecainide (potential for life-threatening cardiac arrhythmia), midazolam, triazolam (potential for prolonged or increased sedation, respiratory depression), simvastatin, lovastatin (increased risk of myopathy including rhabdomyolysis), ergot alkaloids (e.g. ergotamine, dihydroergotamine, ergonovine and methylegonovine, potential for acute ergot toxicity) and rifampicin (risk of severe hepatocellular toxicity).

SQV/r is contraindicated in patients with severe hepatic impairment.

### Pregnancy

Clinical experience in pregnant women is limited. Congenital malformations, birth defects and other disorders (without a congenital malformation) have been

reported rarely in pregnant women who had received SQV in combination with other ARVs. However, so far the available data are insufficient and do not identify specific risks for the unborn child. SQV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Breastfeeding

There are no laboratory animal or human data available on the secretion of SQV in breast milk. The potential for adverse reactions to SQV in nursing infants cannot be assessed, and therefore breast-feeding should be discontinued prior to receiving SQV. It is recommended that HIV-infected women do not breastfeed their infants under any circumstances to avoid transmission of HIV.

### Precautions

*Liver disease:* The safety and efficacy of SQV/r has not been established in patients with significant underlying liver disorders. SQV/r is contraindicated in patients with severe hepatic impairment. Patients with chronic hepatitis B or C and treated with ART are at an increased risk for severe and potentially fatal hepatic adverse events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these drugs.

*Renal impairment:* Renal clearance is only a minor elimination pathway; the principal route of metabolism and excretion for SQV is via the liver. Therefore, no initial dose adjustment is necessary for patients with renal impairment. However, patients with severe renal impairment have not been studied and caution should be exercised when prescribing SQV/r in this population.

*Patients with chronic diarrhoea or malabsorption:* No information on boosted SQV and only limited information on the safety and efficacy of unboosted SQV is available for patients suffering from chronic diarrhoea or malabsorption. It is unknown whether patients with such conditions could receive subtherapeutic SQV levels.

*Haemophilia:* There have been reports of increased bleeding, including spontaneous skin haematomas and haemarthroses, in patients with haemophilia types A and B treated with PIs. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with PIs was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. Patients with haemophilia should therefore be made aware of the possibility of increased bleeding.

*Diabetes mellitus and hyperglycaemia:* New-onset diabetes mellitus, hyperglycaemia or exacerbation of existing diabetes mellitus has been reported in patients

receiving PIs. In some of these patients, the hyperglycaemia was severe and in some cases was also associated with ketoacidosis. Many patients had confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycaemia.

## Dosage

*Adults and adolescents > 16 years*

*In combination with RTV:* The recommended dose of SQV is 1000 mg (5 x 200 mg capsules) two times daily with RTV 100 mg two times daily in combination with other ARVs.

SQV capsules should be swallowed whole and taken at the same time as RTV within 2 hours following a meal.

*In combination with other PIs and NNRTIs:* Dose reduction may be required when SQV/r is administered with some other PIs (e.g. NFV, IDV and delavirdine), since these medicinal products may increase SQV plasma levels.

*Renal and hepatic impairment:* No dosage adjustment is necessary for patients with mild-to-moderate renal or mild hepatic impairment. Caution should be exercised in patients with severe renal or moderate hepatic impairment. SQV/r is contraindicated in patients with severe hepatic impairment.

*Paediatric and elderly patients:* SQV should only be given in combination with RTV, and should not be given as the sole PI. There is only limited information on the safety and efficacy of SQV/r in HIV-infected patients < 16 years and in adults > 60 years.

For children weighing > 25 kg, the approved adult dosing can be used. Capsules should *not* be crushed or opened, but must be swallowed whole.

If possible, monitoring of the SQV level is recommended.

NOTE: To avoid confusion between the different formulations of SQV, prescribers should specify the brand or type of formulation to be dispensed; absorption from gel-filled capsules containing SQV is much greater than from capsules containing SQV mesilate. Treatment should generally be initiated with gel-filled capsules.

## Food effect

Should be taken with food.

## Metabolism

Mainly in the liver

## Interactions

- 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, IDV (in vitro antagonism), lovastatin, midazolam, rifabutin, rifampicin, St John's wort (*Hypericum perforatum*), simvastatin, terfenadine and triazolam.
- SQV levels are increased by clarithromycin, delavirdine (§SQV), grapefruit juice, ketoconazole, LPV (§SQV), NFV (§SQV) and RTV (§SQV).
- SQV levels are decreased by APV, dexamethasone, EFV, NVP (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).
- SQV increases the levels of clarithromycin, NFV, sildenafil and terfenadine.
- SQV decreases the levels of APV and EFV.
- Potential interactions with anticonvulsants, statins, methadone, oral contraceptives, tricyclic antidepressants and oral anticoagulants.

## Adverse effects

The most frequently reported adverse reactions among patients receiving SQV/r as part of their ART were nausea, diarrhoea, fatigue, vomiting, flatulence and abdominal pain. SQV does not alter the pattern, frequency or severity of known major toxicities associated with nucleoside analogues.

Incidences of undesirable effects and marked laboratory abnormalities from the MaxC<sub>min</sub>1 and MaxC<sub>min</sub>2 study are given below (very common ( $\geq 10\%$ ); common ( $\geq 1\%$  and  $< 10\%$ )).

Body system Frequency of reaction	Adverse reactions
Blood and lymphatic system disorders—Common	Anaemia
Gastrointestinal disorders—Very common	Nausea, vomiting
Congenital and familial/genetic disorders—Common	Lipodystrophy (congenital)
Investigations—Very common	ALT increased, AST increased, serum cholesterol increased, serum triglycerides increased, low-density lipoprotein increased, platelet count decreased



Body system Frequency of reaction	Adverse reactions
Investigations—Common	Serum amylase increased, serum bilirubin increased, serum creatinine increased, haemoglobin decreased, lymphocyte count decreased, white blood cell count decreased

See also “Class adverse drug reactions to protease inhibitors” (hyperglycaemia, fat redistribution and hyperlipidaemia), pp 67–68.

### Storage

*Hard capsules:* Should be stored at room temperature (15–30°C). The shelf-life is 3 years.

*Soft capsules:* Store in a refrigerator (2– 8°C). The shelf-life is 2 years.

# 19

## FUSION INHIBITORS

### Enfuvirtide (T-20)

**Class:** Entry inhibitor

#### Available formulations

*Ampoules for injection:* 108 mg T-20 dry powder for the delivery of 90 mg of T-20 when reconstituted with 1.1 ml of sterile water.

1 ml of reconstituted solution contains 90 mg T-20.

#### Uses

T-20 is indicated in combination with other ARV medicinal products for the treatment of HIV-1 infected patients who have received treatment with and failed on regimens containing at least one medicinal product from each of the following ARV classes—PIs, NNRTIs and NsRTIs, or who have intolerance to previous ARV regimens.

#### Contraindications

Systemic hypersensitivity reactions to the active substance or to any of the excipients (inactive ingredients).

#### Pregnancy

There are no adequate and well-controlled studies in pregnant women. Animal studies do not indicate harmful effects with respect to fetal development. T-20 should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

#### Breastfeeding

It is not known whether T-20 is secreted in human milk. Mothers should be instructed not to breastfeed if they are receiving T-20 because of the potential for HIV transmission and any possible undesirable effects in breastfed infants.

#### Precautions

Hypersensitivity reactions have occasionally been associated with therapy with T-20 and, in rare cases, hypersensitivity reactions have recurred on rechallenge. Events included rash, fever, nausea and vomiting, chills, rigors, low blood pressure and raised serum liver transaminases in various

combinations, and possibly primary immune complex reaction, respiratory distress and glomerulonephritis. Patients developing signs/symptoms of a systemic hypersensitivity reaction should discontinue T-20 treatment and should seek medical evaluation immediately. Therapy with T-20 should not be restarted following systemic signs and symptoms consistent with a hypersensitivity reaction considered related to T-20. Risk factors that may predict the occurrence or severity of hypersensitivity to T-20 have not been identified.

*Liver disease:* The safety and efficacy of T-20 has not been specifically studied in patients with significant underlying liver disorders. Patients with chronic hepatitis B and C and treated with ART are at an increased risk for severe and potentially fatal hepatic adverse events. A few patients included in Phase III trials were co-infected with hepatitis B/C. In these patients the addition of T-20 did not increase the incidence of hepatic events. In case of concomitant antiviral therapy for hepatitis B or C, please refer also to the relevant product information for these drugs. Administration of T-20 to non-HIV-1 infected individuals may induce anti-T-20 antibodies that cross-react with HIV gp41. This may result in a false-positive HIV test result with the anti-HIV ELISA test. Patients with reduced hepatic function or those with severe renal impairment have not been studied and only limited data are available in patients with moderate renal impairment. T-20 should be used with caution in these populations.

*Immune reconstitution inflammatory syndrome (IRIS):* In HIV-infected patients with severe immune deficiency at the time of institution of ART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions, or aggravation of symptoms. Typically, such reactions have been observed within the first few weeks or months of initiation of ART. Relevant examples are cytomegalovirus retinitis, generalized and/or focal mycobacterial infections, and *Pneumocystis jiroveci* pneumonia (PCP). Any inflammatory symptoms should be evaluated and treatment instituted when necessary.

## Dosage

*Adults and adolescents  $\geq 16$  years:* 90 mg twice daily injected subcutaneously into the upper arm, anterior thigh or abdomen.

*Elderly:* There is no experience in patients  $>65$  years of age.

*Children  $\geq 6$  years and adolescents:* The experience is based on a very limited number of children. In ongoing clinical trials the dosage regimen in the table below is being used.

Weight (kg)	Dose per bid injection (mg/dose)	Injection volume (90 mg T-20 per ml)
11.0–15.5	27	0.3 ml
15.6–20.0	36	0.4 ml
20.1–24.5	45	0.5 ml
24.6–29.0	54	0.6 ml
29.1–33.5	63	0.7 ml
33.6–38.0	73	0.8 ml
38.1–42.5	81	0.9 ml
≥ 42.6	90	1.0 ml

*Children < 6 years:* Dosage has not been established.

### Food effect

Not applicable

### Metabolism

As a peptide, T-20 undergoes catabolism to its constituent amino acids which are recycled into the body pool. Elimination pathways have not been determined.

### Interactions

No clinically significant pharmacokinetic interactions are expected between T-20 and concomitantly given medicinal products metabolized by CYP450 enzymes.

*Influence of T-20 on metabolism of concomitant medicinal products:* In an in vivo human metabolism study, T-20, at the recommended dose of 90 mg twice daily, did not inhibit the metabolism of substrates by CYP3A4 (dapson), CYP2D6 (debrisoquine), CYP1A2 (caffeine), CYP2C19 (mephenytoin) and CYP2E1 (chlorzoxazone).

*Influence of concomitant medicinal products on T-20 metabolism:* In separate pharmacokinetic interaction studies, co-administration of RTV (potent CYP3A4 inhibitor) or SQV in combination with a booster dose of RTV or rifampicin (potent CYP3A4 inducer) did not result in clinically significant changes of the pharmacokinetics of T-20.

### Adverse effects

*Injection-site reactions:* Injection-site reactions were the most frequently reported adverse reaction and occurred in 98% of the patients. The vast majority of injection-site reactions occurred within the first week of T-20 administration and

were associated with mild-to-moderate pain or discomfort at the injection site without limitation of usual activities. The severity of the pain and discomfort did not increase with treatment duration. The signs and symptoms generally lasted  $\leq 7$  days. Infections at the injection site (including abscess and cellulitis) occurred in 1.5% of patients.

*Other adverse reactions:* The addition of T-20 to background ART generally did not increase the frequency or the severity of the majority of adverse events. The events most frequently reported in patients receiving T-20 + OB (optimized background regimen consisting of 3–5 ARVs selected on the basis of the patient's prior treatment history) were diarrhoea (31.8%) and nausea (22.9%). These events were seen at a lower incidence than in patients who received OB alone: diarrhoea (35.3%) and nausea (24.3%).

## Storage

*Powder:* The powder does not require any special storage conditions.

*After reconstitution:* Store in a refrigerator (2–8°C). Keep the vial in the outer carton in order to protect it from light. The shelf-life is 3 years.

*Solvent:* The solvent does not require any special storage conditions. The shelf-life is 3 years.

*Shelf-life after reconstitution:* Chemical and physical in-use stability has been demonstrated for 48 hours at 5°C when protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

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## ANNEX 1: USEFUL INTERNET LINKS

1. <http://www.who.int/hiv/en/>
2. <http://mednet3.who.int/prequal/outcome.shtml#1>
3. [http://www.who.int/3by5/publications/documents/arv\\_guidelines/en/](http://www.who.int/3by5/publications/documents/arv_guidelines/en/)
4. [http://www.who.int/HIV/Pub/prev\\_care/en/scalingup\\_E.pdf](http://www.who.int/HIV/Pub/prev_care/en/scalingup_E.pdf)
5. <http://www.who.int/medicines/organization/qsm/activities/pilotproc/pilotproc.shtml>
6. <http://www.who.int/medicines/organization/par/edl/expertcomm.shtml>
7. [http://mednet3.who.int/prequal/lists/hiv\\_suppliers.pdf](http://mednet3.who.int/prequal/lists/hiv_suppliers.pdf)
8. <http://www.medscape.com/Home/Topics/AIDS/AIDS.html>
9. <http://www.amfar.org>
10. <http://www.hivandhepatitis.com>
11. <http://www.bnf.org/AboutBNFFrameHowtoUse.htm>
12. <http://www.cdc.gov/hiv/treatment.htm>
13. <http://www.ama-assn.org/special/hiv/hivhome.htm>
14. <http://www.fda.gov/oashi/aids/hiv.html>
15. <http://www.hivatis.org>
16. <http://www.hopkins-aids.edu/>
17. <http://www.aidsmeds.com/>
18. <http://www.aidsmap.com>
19. <http://aids.org>
20. <http://www.thebody.com/>
21. <http://www.hivnat.org/>
22. <http://hivinsite.ucsf.edu/InSite>
23. [http://www.paho.org/English/HCP/HCA/antiretrovirals\\_HP.htm](http://www.paho.org/English/HCP/HCA/antiretrovirals_HP.htm)
24. <http://www.medsafe.gov.nz/>
25. <http://portalprd1.jsi.com/>
26. <http://www.eudra.org/emea.html>
27. <http://www.theglobalfund.org>

Several drug companies that manufacture ARV drugs maintain websites. The exact addresses may be located using search engines.

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## ANNEX 2: USEFUL PUBLICATIONS AND REFERENCES

- (1) WHO-SEARO. *HIV/AIDS in the South-East Asia Region: an update*. New Delhi, India, World Health Organization Regional Office for South-East Asia, April 2002.
- (2) Raffanti S, Haas DW. Antiretroviral agents. In: Hardman JG, Limbird LE, Goodman Gilman A (eds). *Goodman and Gillman's The pharmacological basis of therapeutics*. 10th edition. New York, USA, McGraw-Hill, 2001:1349–80.
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- (4) Dolin R, Masur H, Saag MS (eds). *AIDS therapy*. Philadelphia, USA, Churchill Livingstone, 1999.
- (5) Bartlett JG, Gallant JE. *Medical management of HIV infection 2001–2002*. Baltimore, USA, Johns Hopkins University, 2001.
- (6) Gilbert D, Moellering R, Sande M (eds). *Stanford guide to HIV/AIDS therapy 2001*. 10th edition. Hyde Park, USA, Antimicrobial Therapy, Inc., 2001.
- (7) Piscitelli SC, Gallicano HD. *Interactions among drugs for HIV and opportunistic infections*. *N Engl J Med* 2001, 344:984–96.
- (8) J Fellay et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001, 358:1322–7.
- (9) UNICEF, UNAIDS, WHO and MSF. *Sources and prices of selected drugs and diagnostics for people living with HIV/AIDS*. Geneva, World Health Organization, June 2005.
- (10) *British National Formulary*. 43rd edition. London, UK, British Medical Association and the Royal Pharmaceutical Society of Great Britain, March 2002.
- (11) Narain JP, Chela C, van Praag E (eds). *Planning and implementing HIV/AIDS care programmes: a step-by-step approach*. New Delhi, India, World Health Organization Regional Office for South-East Asia, 2000 (SEA/AIDS/106).
- (12) Back D et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS* 2002, 16 (suppl 1):S5–S37.

- (13) World Health Organization. *Management of HIV infection and antiretroviral therapy in adults and adolescents: a clinical manual*. New Delhi, World Health Organization Regional Office for South-East Asia, 2006.
- (14) World Health Organization. *Management of HIV infection and antiretroviral therapy in infants and children: a clinical manual*. New Delhi, World Health Organization Regional Office for South-East Asia and United Nations Children's Fund, 2006.
- (15) World Health Organization. *Antiretroviral therapy for HIV infection in adults and adolescents in resource-limited settings: towards universal access*. Geneva, World Health Organization, 2006.
- (16) World Health Organization. *Antiretroviral therapy for HIV infection in infants and children in resource-limited settings: towards universal access*. Geneva, World Health Organization, 2006.
- (17) World Health Organization. *WHO HIV prevention and treatment guidelines*. Geneva, World Health Organization, 2006.
- (18) World Health Organization. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants in resource-limited settings: towards universal access. Recommendations for a public health approach*. Geneva, World Health Organization, 2006.
- (19) World Health Organization. *HIV/AIDS treatment and care for injecting drug users in Asia: a guide to essential practice*. World Health Organization Regional Office for South-East Asia and Regional Office for the Western Pacific, draft 2006.



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## ANNEX 3:

# RECOMMENDED STORAGE CONDITIONS AND SHELF-LIVES FOR ANTIRETROVIRALS AND FIXED-DOSE COMBINATIONS

In the table below room temperature refers to 15–30 degree Celsius (°C). Refrigeration refers to 2–8°C.

Note that the information in this table is indicative only; in case of difference, the instructions and recommendations from the manufacturer of the concerned product supersede the information below and should be followed/relied on.

Generic name	Dosage form	Storage conditions	Shelf-life
Abacavir (ABC)	Tablets	Room temperature	3 years
	Oral solution	Room temperature, may be refrigerated but DO NOT FREEZE	2 years
Abacavir (ABC) + lamivudine (3TC) + zidovudine (AZT)	Tablets	Room temperature	2 years
Amprenavir (APV)	Oral suspension	Room temperature	2 years
	Capsules	Room temperature	18 months
Atazanavir (ATV)	Capsules	Room temperature	2 years
Didanosine (ddI)	Tablets and capsules	Room temperature	2 years
	Powder for oral solution	Room temperature. The ddI reconstituted mixture may be stored up to 30 days in a refrigerator (2–8°C). Discard any unused portion after 30 days.	Check the product label/ packet insert
Efavirenz (EFV)	Capsules	Room temperature	2–3 years depending on manufacturer/ packaging. Check the product label/ packet insert

Generic name	Dosage form	Storage conditions	Shelf-life
	Oral solution	Room temperature. The oral solution should be used within one month of first opening the bottle.	3 years
	Tablets	Room temperature	2 years
Emtricitabine (FTC)	Tablets	Room temperature	Check the product label/ packet insert
	Capsules	Room temperature	2 years
	Oral solution	Should be refrigerated. After first opening of the bottle, the shelf-life is 45 days. Do not store the opened bottle above 25 °C.	3 years
Emtricitabine (FTC) + tenofovir (TDF)	Tablets	Room temperature	2 years
Enfuvirtide (T-20)	Powder for injection	<p>Does not require any special storage conditions. After reconstitution: Store in a refrigerator (2–8 °C). Keep the vial in the outer carton in order to protect from light. Chemical and physical in-use stability has been demonstrated for 48 hours at 5 °C when protected from light. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2–8 °C, unless reconstitution has taken place in controlled and validated aseptic conditions.</p> <p>The solvent does not require any special storage conditions.</p>	<p>3 years</p> <p>(solvent)</p>

Generic name	Dosage form	Storage conditions	Shelf-life
Fosamprenavir (Fos-APV)	Oral suspension	Room temperature, or 2–30°C. Do not freeze. Discard 28 days after first opening.	2 years
	Tablets	Room temperature	3 years
Indinavir (IDV)	Capsules	Room temperature	2-3 years. Check the product label/ packet insert
Lamivudine (3TC)	Tablets	Room temperature	2 years
	Film-coated tablets	Room temperature	3 years
	Oral powder	Room temperature	2 years
Lamivudine (3TC) + stavudine (d4T)	Tablets	Room temperature	2 years
Lamivudine (3TC) + zidovudine (AZT)	Tablets	Room temperature	2–3 years depending on the manufacturer. Check the product label/ packet insert
Lamivudine (3TC) + nevirapine (NVP) + stavudine (d4T)	Tablets	Room temperature	18 months to 2 years depending on the manufacturer/ packaging. Check the product label/ packet insert
Lamivudine (3TC) + nevirapine (NVP) + zidovudine (AZT)	Tablets	Room temperature	Check the product label/ packet insert
Lamivudine (3TC) + zidovudine (AZT) + efavirenz (EFV)	Tablets	Room temperature	3 years

Generic name	Dosage form	Storage conditions	Shelf-life
Lopinavir/ritonavir (LPV/r)	Capsules	Store at 2–8°C (refrigerator) until dispensed. Avoid exposure to excessive heat. If stored at room temperature up to 25°C, use capsules within 6 weeks.	2 years
	Heat-stable tablets	Room temperature	2 years
	Oral suspension	Store oral suspension at 2–8°C (refrigerator) until dispensed. Avoid exposure to excessive heat. If stored at room temperature up to 25°C, use suspension within 2 months.	2 years
Nelfinavir (NFV)	Powder for oral suspension	Room temperature	2–3years depending on the manufacturer. Check the product label/packet insert
	Tablets	Room temperature	2 years
Nevirapine (NVP)	Oral suspension	Room temperature	2 years. Shelf-life after opening the bottle is 2 months only.
	Tablets	Room temperature	2 years
Ritonavir (RTV)	Oral solution	Room temperature (do not refrigerate)	6 months
	Capsules	Store in refrigerator (2–8°C) until they are dispensed to the patient. Refrigeration by the patient is not required if used within 30 days and stored below 25°C.	2 years
Saquinavir (SQV)	Hard gelatin capsules	Room temperature	3 years
	Soft gelatin capsules	Store in a refrigerator	2 years
Stavudine (d4T)	Capsules	Room temperature	2 years

Generic name	Dosage form	Storage conditions	Shelf-life
	Powder for oral solution	Room temperature. After reconstitution, the oral solution may be stored in the original bottle with the lid tightly closed for up to 30 days under refrigeration (2–8°C). Discard any unused portion after 30 days.	2 years
	Extended-release capsules	Room temperature	2 years
Tenofovir (TDF)	Tablets	Room temperature	3 years
Zidovudine (AZT)	Capsules	Room temperature	3–5 years depending on the manufacturer. Check the product label/packet insert
	Tablets	Room temperature	2–3 years. Check the product label/packet insert
	Oral solution/syrup	Room temperature	2–3 years depending of the manufacturer. Check the product label/packet insert
	IV solution: (concentrate for solution for infusion)	Room temperature	3 years





This document is a compilation of current facts and product information about antiretroviral drugs that are commonly used for the treatment of HIV infection in resource - constrained settings. For each drug, information is provided 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, reports presented at international conferences, information from medicines regulatory authorities and national guidelines for antiretroviral treatment of different countries and from websites dedicated to the treatment of HIV infection.

This compilation is meant to be a supplementary and easily accessible source of information for prescribers.



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