

TDM monograph Atazanavir

Reyataz[®]:

Summary

Indication:	HIV infection Off-label indications: none Indications TDM: Prevention of virological failure Evaluation of toxicity
Sample material:	EDTA plasma
Time of sampling:	Trough sample, i.e. prior to next dose
Storage conditions:	2-8 °C (during transport) / -40 °C (storage until analysis)
Interpretation:	Target trough concentration: > 0.15 mg/L to prevent virological failure < 0.85 mg/L in case of unpleasant (asymptomatic) hyperbilirubinemia
Evidence level:	4

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Introduction

Atazanavir (ATV) was initially developed (and approved) as an unboosted HIV-protease inhibitor (400mg QD), but nowadays it is no longer preferred to be given as a single agent because of its low absorption and rapid elimination. It always needs to be boosted by a CYP3A inhibitor such as ritonavir (RTV) or cobicistat (COBI). Boosters do not have antiviral activity.

Atazanavir+ritonavir is often abbreviated as ATV/r.

Atazanavir+cobicistat is often abbreviated as ATV/c (not available in the Netherlands).

Dosing guidelines

Indication (1)

Atazanavir, co-administered with low dose ritonavir, is indicated for the treatment of HIV-1-infected patients in combination with other antiretroviral medicinal products.

The adult dose is atazanavir 300mg + 100mg of ritonavir (or 150mg of cobicistat) with food.

Dosing guidelines in children and adolescents (1)(2)

Children weighing at least 35kg can take the adult dose.

Children weighing 15 – 35kg can take 200mg of atazanavir with 100mg of ritonavir (or 150mg of cobicistat)

Children 3 months of age and older weighing at least 5kg can take oral powder of atazanavir with ritonavir solution/capsules:

Table 1: Dose of REYATAZ oral powder with ritonavir for paediatric patients^a (at least 3 months of age and weighing at least 5 kg)

Body weight (kg)	REYATAZ once daily dose	ritonavir once daily dose
at least 5 to less than 15	200 mg (4 sachets ^b)	80 mg ^c
at least 15 to less than 35	250 mg (5 sachets ^b)	80 mg ^c
at least 35	300 mg (6 sachets ^b)	100 mg ^d

^a The same recommendations regarding the timing and maximum doses of concomitant proton pump inhibitors and H₂-receptor antagonists in adults also apply to paediatric patients (see section 4.5).

^b Each sachet contains 50 mg of atazanavir.

^c Ritonavir oral solution.

^d Ritonavir oral solution or capsule/tablet.

Dosing guidelines in patients with altered pharmacokinetics (1)

No dosage adjustment is needed. Atazanavir with ritonavir is not recommended in patients undergoing haemodialysis

Atazanavir with ritonavir has not been studied in patients with hepatic impairment. Atazanavir with ritonavir should be used with caution in patients with mild hepatic impairment. Atazanavir with ritonavir must not be used in patients with moderate to severe hepatic impairment.

See also (3)

Page 84: Dose adjustment of ARVs for impaired renal function

Page 93: Dose adjustment of ARVs for impaired hepatic function

Indications/Criteria for TDM

The primary indication for TDM of ATV is the prevention of virological failure. As atazanavir plasma levels are correlated with (asymptomatic) increases in bilirubin, TDM of atazanavir can be used to manage hyperbilirubinemia when patients are suffering from unpleasant discolouring of skin and eyes.

Other potential indications for TDM can be:

- Potential drug concentration-related toxicity (other than hyperbilirubinemia)
- Special patient populations (pregnancy, children)
- Drug-drug interactions
- Suspicion of nonadherence
- Etc.

Reference values

Target trough concentration:

> 0.15 mg/L to prevent virological failure

< 0.76 mg/L in case of unpleasant (asymptomatic) hyperbilirubinemia

Efficacy

In an Italian study that is only available in abstract form, Gonzalez de Requena et al. described a study in 51 patients of which 59% used “boosted atazanavir” and 33% had not used a PI before (4). The virological response after 24 weeks was strongly correlated with the atazanavir trough level, with the cut-off value determined by an ROC analysis at 0.15 mg/L. Patients with a trough level below this value had a 37.5% virological response vs. 81% if the trough level was >0.15 mg/L ($p=0.027$).

A PK/PD study that was part of the BMS-089 study explored possible relationships between atazanavir trough level and antiviral response in treatment-naïve patients (5). In this study, the atazanavir dosage without ritonavir (400mg QD) was compared to the atazanavir/ritonavir combination (300/100mg QD), of course in combination with an NRTI backbone. A clear concentration-effect relationship was found, but unfortunately no cut-off point is established. A table shows that the highest chance of response was found if the trough level is > 0.15 mg/L.

The data also show that up to 50% of patients on “unboosted” atazanavir can have a trough level < 0.15 mg/L, while this was found in almost no one using atazanavir/ritonavir. In line with this is also the slightly better antiviral response found in the main study for atazanavir/ritonavir compared to atazanavir alone. These data also make it clear that it is very difficult to find a cut-off point for atazanavir if only patients using atazanavir/ritonavir are included in a study, because everyone has a level above this 0.15 mg/L and (therefore) a good therapy response. A large proportion of patients with levels < 0.15 mg/L still can have a good response, but the chance of failure is greater than when the trough level is > 0.15 mg/L.

Goutelle et al. performed an analysis of patients on “unboosted” atazanavir who received this regimen as maintenance treatment (6). They confirmed the cut-off value of 0.15 mg/L: patients below had a 3.53 higher chance of virological failure than patients with a trough level > 0.15 mg/L.

A theoretical approach can also be followed to calculate a target value for optimal virological response: the highest IC_{90} value that has been determined in cell cultures is 15 nM (7) which corresponds to 0.012 mg/L. Atazanavir is approximately 14% unbound to protein; therefore, the in vitro IC_{90} should be multiplied by a factor of 7: $7 \times 0.012 = 0.084$ mg/L. This is no more than a factor of 2 away from the above-mentioned target value of 0.15 mg/L and thus supports the clinical relevance for PI-naïve patients.

Relationship with occurrence of side effects

A number of studies have been presented on the possible relationship between high atazanavir plasma levels and an increase in total bilirubin (7-10). Despite differences in follow-up and definition of endpoints, the cut-off points found are close to each other. The highest value was 0.76 mg/L. 2.0 mg/l has been mentioned as a cut-off value for a C12h (10).

Discolouring of skin and eyes can have a stigmatizing effect on patients using atazanavir, and if this happens, should be managed. Targeting trough levels below 0.76 mg/L (but above 0.15 mg/L) is then a reasonable approach.

Toxicity (1)

Among patients who received atazanavir 400 mg once daily or atazanavir 300 mg with ritonavir 100 mg once daily, the only adverse reactions of any severity reported very commonly with at least a

possible relationship to regimens containing atazanavir and one or more NRTIs were nausea (20%), diarrhoea (10%), and jaundice (13%). Among patients receiving atazanavir 300 mg with ritonavir 100 mg, the frequency of jaundice was 19%.

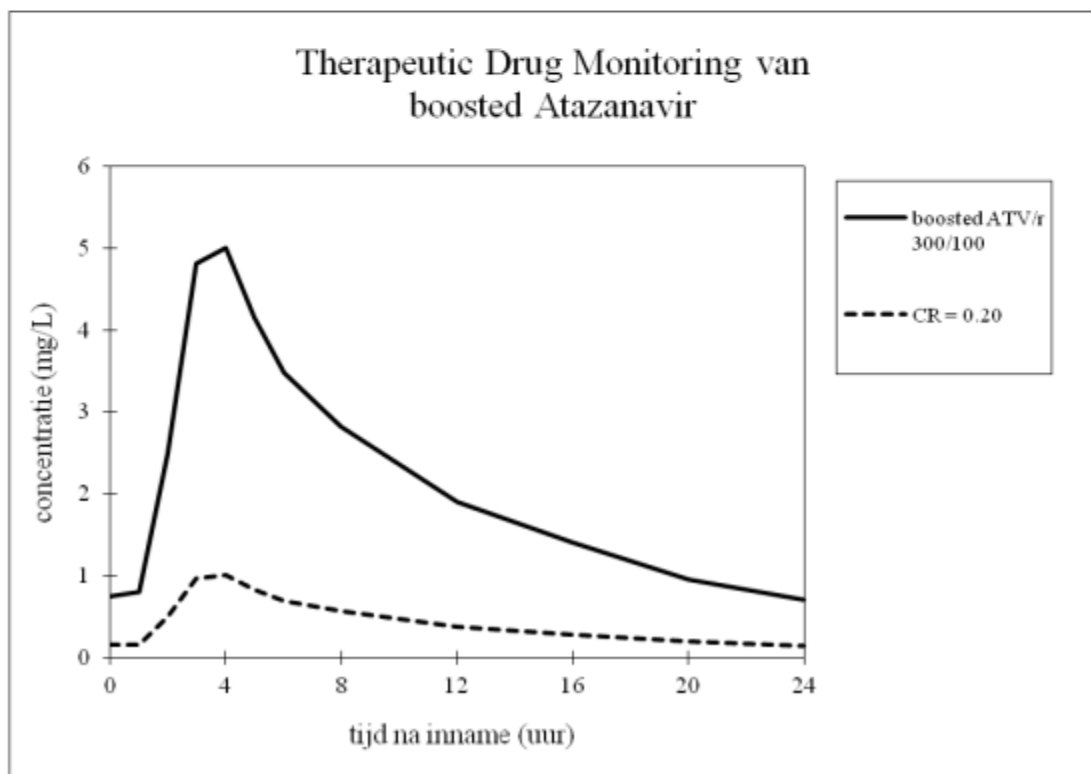
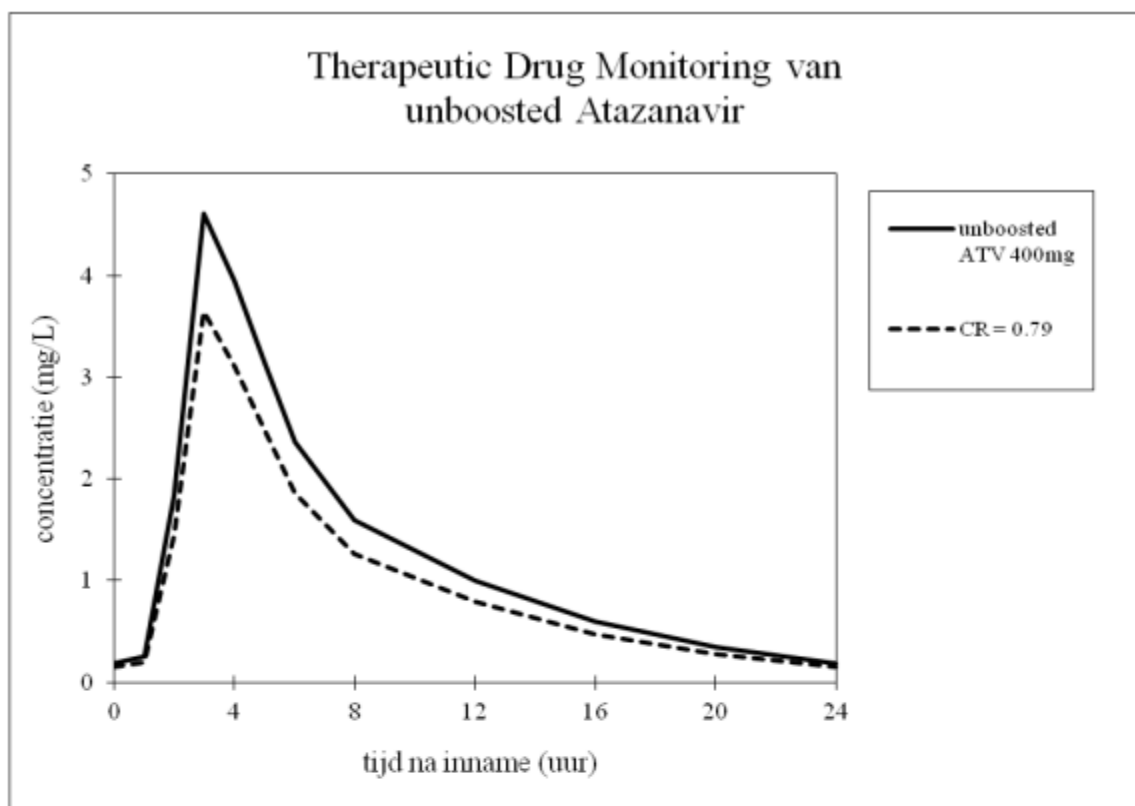
Sampling conditions

A TDM sample should be taken in an EDTA tube without gel. Samples should be stored at -40 °C pending analysis.

Additional information concerning the interpretation of results

tijd (uur)	unboosted ATV 400mg	CR = 0,79	boosted ATV/r 300/100	CR = 0,20
0	0,19	0,15	0,74	0,15
1	0,25	0,20	0,80	0,16
2	1,84	1,45	2,49	0,50
3	4,61	3,64	4,82	0,96
4	3,94	3,11	5,01	1,00
5	3,15	2,49	4,15	0,83
6	2,36	1,86	3,48	0,70
8	1,60	1,26	2,83	0,57
12	1,00	0,79	1,90	0,38
16	0,60	0,47	1,40	0,28
20	0,35	0,28	0,95	0,19
24	0,19	0,15	0,70	0,14

CR = concentration ratio. All concentrations are expressed in mg/L.



Background information [extended]

Pharmacodynamics (1)

Atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

Antiviral activity in vitro: atazanavir exhibits anti-HIV-1 (including all clades tested) and anti-HIV-2 activity in cell culture.

Pharmacokinetics (1)

The pharmacokinetics of atazanavir were evaluated in healthy adult volunteers and in HIV-infected patients; significant differences were observed between the two groups. The pharmacokinetics of atazanavir exhibit a non-linear disposition.

Absorption: in HIV-infected patients (n = 33, combined studies), multiple dosing of atazanavir 300 mg once daily with ritonavir 100 mg once daily with food produced a geometric mean (CV%) for atazanavir, C_{max} of 4466 (42%) ng/mL, with time to C_{max} of approximately 2.5 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC was 654 (76%) ng/mL and 44185 (51%) ng•h/mL, respectively.

In HIV-infected patients (n = 13), multiple dosing of REYATAZ 400 mg (without ritonavir) once daily with food produced a geometric mean (CV%) for atazanavir C_{max} of 2298 (71) ng/mL, with time to C_{max} of approximately 2.0 hours. The geometric mean (CV%) for atazanavir C_{min} and AUC were 120 (109) ng/mL and 14874 (91) ng•h/mL, respectively.

Food effect: co-administration of atazanavir and ritonavir with food optimises the bioavailability of atazanavir. Co-administration of a single 300-mg dose of REYATAZ and 100-mg dose of ritonavir with a light meal resulted in a 33% increase in the AUC and a 40% increase in both the C_{max} and the 24 hour concentration of atazanavir relative to the fasting state. Co-administration with a high-fat meal did not affect the AUC of atazanavir relative to fasting conditions and the C_{max} was within 11% of fasting values. The 24-hour concentration following a high-fat meal was increased by approximately 33% due to delayed absorption; the median T_{max} increased from 2.0 to 5.0 hours. Administration of REYATAZ with ritonavir with either a light or a high fat meal decreased the coefficient of variation of AUC and C_{max} by approximately 25% compared to the fasting state. To enhance bioavailability and minimise variability, atazanavir is to be taken with food.

Distribution: atazanavir was approximately 86% bound to human serum proteins over a concentration range of 100 to 10,000 ng/mL. Atazanavir binds to both alpha-1-acid glycoprotein (AAG) and albumin to a similar extent (89% and 86%, respectively, at 1,000 ng/mL). In a multiple-dose study in HIV-infected patients dosed with 400-mg of atazanavir once daily with a light meal for 12 weeks, atazanavir was detected in the cerebrospinal fluid and semen.

Metabolism: studies in humans and in vitro studies using human liver microsomes have demonstrated that atazanavir is principally metabolised by CYP3A4 isozyme to oxygenated metabolites. Metabolites are then excreted in the bile as either free or glucuronidated metabolites. Additional minor metabolic pathways consist of N-dealkylation and hydrolysis. Two minor metabolites of atazanavir in plasma

have been characterised. Neither metabolite demonstrated in vitro antiviral activity.

Elimination: following a single 400 mg dose of ¹⁴C-atazanavir, 79% and 13% of the total radioactivity was recovered in the faeces and urine, respectively. Unchanged drug accounted for approximately 20% and 7% of the administered dose in the faeces and urine, respectively. Mean urinary excretion of unchanged drug was 7% following 2 weeks of dosing at 800 mg once daily. In HIV-infected adult patients (n = 33, combined studies) the mean half-life within a dosing interval for atazanavir was 12 hours at steady state following a dose of 300 mg daily with ritonavir 100 mg once daily with a light meal

Pharmacogenetics

Atazanavir can cause hyperbilirubinemia (not associated with liver injury) leading to jaundice, which is a common cause of drug discontinuation. Individuals with 2 decreased-function alleles for UGT1A1 are most likely to experience jaundice leading to atazanavir discontinuation, although this can occur despite the individual having a reference UGT1A1 genotype. The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that when an individual is a known UGT1A1 poor metabolizer, an alternative therapy should be considered particularly when jaundice is of concern to the individual (11)

Interactions

See (12)

www.hiv-druginteractions.org

PK parameters

	F (%)	Cl (L/h⁻¹)	Vd (L/kg)	t_{1/2} (h⁻¹)	Protein binding	Tmax (h)	Ref.
HIV-infected patients	Not assessed			12	86%	5	(1)

Population models

Population	Model	K_{abs} (h⁻¹) / F	Vd (L) / F	K_{elm} (h⁻¹) / F	CL (L/h⁻¹) / F	Ref.
HIV-infected patients		2.0	95.7		11.7	(13)

Literatuur

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Colophon

This guideline has been constituted by David Burger, PharmD, PhD
Date: January 8, 2025

Appendices

Not applicable

Revision

This guideline has been revised by David Burger, PharmD, PhD] under the auspices of TDM, Toxicology and Pharmacogenetics committee (TTF) of the Dutch Association of Hospital Pharmacists (NVZA) and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology (IATDMCT)

The guidelines was updated based on most recent literature and translated to English [Jan 8, 2025]