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German-Austrian Recommendations for the Antiretroviral Therapy of HIV-infection

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INTRODUCTION

The availability and application of effective antiretroviral combination therapies have now almost become routine. More than 20 antiretroviral substances in four classes have been approved. Although an almost incalculable number of combinations can be conceived, it must be stressed, that only a small number of the theoretically possible combinations are actually applicable.

As a result of the broad therapeutic armamentarium, HIV infection can be better treated. However, the decisions to start, monitor and change therapy have become even more difficult because the indication for treatment, the selection of the most suitable therapy for an individual, the information and counselling of the patient, and the monitoring of the success of treatment all demand a high level of knowledge and experience. This guideline evaluates the indication and selection of the initial antiretroviral therapy for HIV infection.

BASICS

Inhibition of viral replication by an antiretroviral therapy prevents disease progression, leads to a regression of HIV-associated symptoms, and enables a clinically relevant immune reconstitution [1-4]. The prognosis for HIV-infected patients has improved dramatically as a result [5]. The improved efficacy of currently available antiretroviral combination therapies and the side effects of such therapies have renewed discussion about the ideal time-point to initiate therapy for HIV infection. The duration of an already initiated therapy has now been markedly prolonged because of the satisfactory efficacy, while the possibility of eradicating the virus nevertheless appears increasingly unlikely. The "ideal" time-point for the initiation of therapy has not been defined up until now in any randomised trial, and this is unlikely to change in the near future.

There are good arguments to initiate therapy as early as possible as there are for deferring therapy to as late as possible, without any clear evidence in favour of one of these approaches.

Arguments for an early initiation of therapy include:

- HIV is an infectious disease, and anti-infective therapy is usually started as early as possible;
- With long-lasting replication of HIV, a point of no return might be passed for the immune system, after which a restoration of the immune system is no longer possible;
- A long-lasting replication leads to virus mutation due to the selection pressure of the immune system so that a large number of quasi species and transient mutations arise that may be more difficult to control by antiretroviral therapy and the immune response.
- Reduction of the risk of transmission ;
- The risk of certain serious clinical complications of the HIV infection (e.g. HIV-associated lymphoma, cervical or anal carcinoma) might be reduced with an early initiation of therapy.

Arguments for a late initiation of therapy are:

- Errors in the intake of antiretrovirals are probable with the current complex antiretroviral combinations and might lead to an ineffectiveness of later therapy;
- Daily intake of medications entails a clear physical and psychological burden, particularly on asymptomatic patients, who may experience a reduction in quality of life as a consequence;
- A clinical improvement and immune reconstitution can still be observed if therapy is initiated in an advanced stage of HIV infection;
- Unlike other infectious diseases, an eradication of the pathogen is currently not possible, and it is not possible to induce a durable (permanent) control of virus replication that persists after stopping therapy

Broad consensus exists on the objective of preventing the progression of an asymptomatic HIV-infection for as long as possible as well as regarding the initiation of therapy before irreversible damage to the immune system occurs. The recommendations provided here are based on the evaluation of randomised controlled trial using clinical end points (I), randomised controlled trials with laboratory markers as end points (II), and the evaluation of other clinical pathophysiological and pharmacological data by expert committees (III, see Table 1). With the remaining uncertainties, especially regarding the optimal time-point to initiate therapy, even a broad consensus may still be associated with a certain degree of error.

Randomised trials with clinical end points are the preferred basis for therapeutic recommendations in medicine. Because of the high correlation between the most important surrogate markers (the development of HIV-RNA in plasma, the development of CD4 lymphocytes) and the clinical end points in drug registration trials for the first protease inhibitors at the start of 1996, registration trials for HIV infection are usually no longer carried out as clinical end point trials, but instead as surrogate marker trials.

Conditions for registration/approval have been defined explicitly by the FDA and the EMEA, and as a result of these, clinical end point trials are now only carried out in exceptional circumstances.

For new substances to be accepted as part of an initial therapy, data should be available from approval studies over a period of at least 2 years since they were started.

As such, evidence class I trials are usually older trials, with already outdated therapeutic schemes, and evidence class I trials do not carry as much weight in influencing current recommendations as do evidence class II trials. For many indications relating to the therapy of HIV-infection the most realisable is a grading as AII. Many open questions will not be answered by randomised trials in the near future: long-term studies are hard to realise in a field that is undergoing such rapid changes in the mode of therapy, and this applies particularly to placebo-controlled trials with clinical end points.

Table 1. Classification of therapeutic recommendations.

Classification of therapeutic recommendations	I	II	III
	On the basis of at least one randomised trials with clinical end points *	On the basis of surrogate marker-trials	According to expert opinion
A Unambiguous recommendation	A I	A II	A III
B Generally advisable	B I	B II	B III
C Justifiable	C I	C II	C III
D Generally inadvisable	D I	D II	D III
E Unambiguously inadvisable	E I	E II	E III

*Clinical end point trials are no longer carried out due to the changed conditions for new substance approval demanded by the FDA and EMEA

General Therapeutic Principles

A decrease in morbidity and mortality can already be achieved by reducing virus burden by approx. 1 - 2 log10. From our current viewpoint, such an unacceptably small reduction in virus burden under therapy leads rapidly to a selection of resistant virus mutants or virological therapeutic failure so that the risk of clinical progression increases. A (almost) complete suppression of viral replication extends the therapeutic effect and in this way ensures a long-lasting risk reduction. This demands a high antiviral activity of the drug combination employed [6, 7].

The goal of an initial antiretroviral therapy is to reduce the virus burden to below the current detection limit of 20-50 HIV-RNA copies/ml. Depending on individual circumstances (e.g. long-standing previous treatment with a suboptimal therapeutic regime, the existence of multiple resistance) it may become necessary to increase the number of drugs in a combination or to agree upon less strict but still realisable therapeutic goals while taking into account the patient's history.

When deciding on treatment initiation, disadvantages and advantages have to be weighed in a dialogue between the HIV specialist and his/her well-informed patient. This applies particularly to patients with high CD4+ cell numbers (Table 3). Several studies have shown that taking medication regularly as prescribed is an essential precondition for the success of an antiretroviral therapy [9, 10]. This high degree of compliance must be achieved through co-operation between the physician and his/her patient.

Indications for Therapy

Symptomatic Patients

In patients with symptoms due to HIV-infection antiretroviral therapy markedly slows down the progression of HIV infection (progression to clinical manifestations C and B of the CDC clinical classification), independently of immune status and virus burden. In addition, HIV-associated symptoms and manifestations can be positively influenced by antiretroviral therapy. As such, therapy is indicated, and all patients belonging to these groups should be urgently recommended to initiate therapy (see initial therapeutic schemes) (AI).

Asymptomatic Patients

No study has yet been able to answer the question concerning the optimal time-point for starting treatment in asymptomatic patients. It was determined from a range of cohort studies that an increased morbidity and mortality has to be expected if CD4 cell number fall below 200 cell/µl (15% CD4). A decrease of CD4 cell number below this limit should therefore be avoided urgently [11]. Asymptomatic patients with less than 200 CD4+/µl have a clear risk of immunological and clinical progression independent of the extent of viral replication that can be decreased by antiretroviral therapy [12, 13]. Therapy for these patients is therefore rational and clearly indicated (AI).

The thresholds for the number of CD4+ lymphocytes and HIV viral load at which a therapy should be started can only be formulated roughly from our current state of knowledge. For CD4+ lymphocytes the threshold for initiation of therapy lies within the range between 200 and 350 CD4+/µl or in percentages of CD4+ lymphocytes between 15-20% of the total lymphocytes. The viral load should also be considered as an additional parameter for determining the urgency of treatment within this CD4+ cell corridor. The higher the viral load, the higher the risk of immunological and clinical progression, and the more unambiguous is the indication for therapy. This applies particularly where there are clear trends in increasing HIV-RNA levels and decreasing CD4 lymphocytes over time [5,11]. The kinetics of the first three measurements of viral load and helper cells can also be helpful for the decision between initiation of therapy and a wait and see approach respectively. A stable course rather justifies a wait and see approach than a case with three deteriorating values.

Table 2. Antiretroviral substance classes, substances and dosing.

Substance as well as substance group	**Trade name**	**Most important adverse effects**	**Dietary regulations**	**Dosage form**	**Dose***
Reverse transcriptase inhibitors -- nucleoside analogues		hepatic steatosis, rarely lactate acidosis, lipodystrophy syndrome§			
Abacavir	Ziagen	Hypersensitivity syndrome		300 mg tablets Juice	2 x 300 mg
Didanosine	Videx	Pancreatitis, neuropathy, lipoatrophy	To be taken on an empty stomach	400 mg capsules 250 mg capsules 125 mg capsules powder	> 60 kg BW: 1x 400 mg < 60 kg BW: 1x 250 mg or 2x 125 mg
Emtricitabine	Emtriva	Headache, anaemia		200 mg capsules 10 mg/ml juice	1 x 200 mg
Lamivudine	Epivir	Headache		300 mg tablets 150 mg tablets Solution	1 x 300 mg or 2 x 150 mg
Stavudine	Zerit	Neuropathy, pancreatitis, lipoatrophy		40 mg capsules 30 mg capsules	BW >60kg: 2 x 40 mg BW <60kg: 2 x 30 mg
Zalcitabine	Hivid	Neuropathy, oral ulcers		0,75mg tablets	3 x 0.75mg
Zidovudine	Retrovir	Neutropenia, anaemia, myopathy, lipoatrophy (minor)		250 mg capsules Juice	2x 250 mg
Combination preparation: Lamivudine+ Zidovudine	Combivir	Headache, neutropenia, anaemia, myopathy		Tablets (150 mg/300 mg)	2x (150 mg+300 mg)
Combination preparation: Lamivudine+ Zidovudine+ Abacavir	Trizivir	Headache, neutropenia, anaemia, myopathy, hypersensitivity-syndrome		Tablets (150 mg/300 mg/300 mg)	2 x 150mg+ 2 x 300mg+ 2 x 300mg
Nucleotide analogues					
Tenofovir	Viread	Gastrointestinal complaints (diarrhoea, nausea), rare renal functional disorders		Tablets 300 mg	1 x 245mg
Protease inhibitors**		Glucose intolerance, disorders in lipid metabolism, lipodystrophy syndrome§ Gastrointestinal complaints			
Amprenavir	Agenerase	Diarrhoea, headache, drug exanthema	To be taken on an empty stomach and with reduced fat intake	150 mg capsules Juice	2x1200mg Recommendation in combination with Ritonavir: Amprenavir: 2 x 600mg Ritonavir: 2 x 100mg
Fosamprenavir	Telzir (USA: Lexiva)	Diarrhoea		700 mg tablets	2x1400mg in combination with Ritonavir Fosamprenavir: 1x1400mg Ritonavir: 1x200mg or Fosamprenavir: 2x700mg Ritonavir: 2x100mg
Atazanavir°	Reyataz	Hyperbilirubinaemia, diarrhoea, headache	To be taken at mealtimes	100 mg capsules 150 mg capsules 200 mg capsules	1x400mg in combination with Ritonavir Atazanavir: 1x300mg Ritonavir: 1x100mg

Substance as well as substance group	Trade name	Most important adverse effects	Dietary regulations	Dosage form	Dose*
Indinavir	Crixivan	Nephrolithiasis, hyperbilirubinaemia, Dry skin and mucosa, Onychodystrophy	To be taken on an empty stomach and with reduced fat intake	400 mg capsules	As a mono PI 3 x 800mg Recommendation in combination with Ritonavir: Indinavir: 2 x 400mg Ritonavir: 2 x 100mg
Lopinavir+Ritonavir	Kaletra	Disorders in lipid metabolism, nausea, diarrhoea	To be taken at mealtimes	Capsules (133 mg/33 mg) Solution	2 x 400mg + 2 x 100mg
Nelfinavir	Viracept	Diarrhoea, nausea	Not to be taken on an empty stomach	625 mg tablets Powder	2 x 1250mg
Ritonavir	Norvir	Diarrhoea, nausea, hypertriglyceridaemia		100 mg capsules Juice	Almost exclusively used to boost other PIs. 2x100mg
Saquinavir	Invirase*** Fortovase	Diarrhoea, nausea (mostly mild)	To be consumed with a protein and fat rich meal	200 mg capsules	3 x 1200mg Recommendation in combination with: Ritonavir Saquinavir: 2 x 1000mg Ritonavir: 2 x 100mg
Reverse transcriptase inhibitors – non-nucleoside		Reactions to medication			
Delavirdine	Rescriptor	Drug exanthema		200 mg tablets	3 x 400mg
Efavirenz^	Sustiva, Stocrin	Psychotropic SE; Drug exanthema		200 mg capsules 600 mg tablets	1 x 600mg
Nevirapine****	Viramune	Drug exanthema, hepatotoxicity		200 mg tablets	2 x 200mg 14 days 1 x 200mg, then 2x 200 mg
Fusion inhibitors		Reactions to medication			
Enfuvirtide°	Fuzeon	Local indurations at the injection site		90mg ampoules	2 x90mg subcutaneous

* Normal kidney function, body weight >60kg;

** All protease inhibitors are inhibitors of cytochrome P450, Ritonavir is the most potent inhibitor, and some isoenzymes are also induced by Ritonavir;

*** Only to be employed in combination with Ritonavir;

**** If necessary, the Lopinavir/Ritonavir dose with PI pre-treated patients may be increased to 533/133mg in combination with Efavirenz or Nevirapine. In general, dose adaptations and drug monitoring should be considered with NNRTIs and PIs because of drug interactions when they are applied in combination.

^ Different trade names in Germany and Austria;

° Not yet approved for initial therapy

§ The pathogenesis of lipodystrophy syndrome still remains to be determined. Lipoatrophy (disappearance of subcutaneous adipose tissue) appears to be primarily due to mitochondrial toxicity of nucleoside analogues, while lipo-accumulation is probably a side effect of protease inhibitors.

Among patients with a CD4 cell count higher than 350/µl, lower than 500/µl and a high viral load (HIV-RNA values above 50,000-100,000 copy/ml are considered as comparably high), introduction of therapy is associated particularly with a clear improvement in the surrogate markers. In such cases the indication for therapy is unclear, but is recommended by some experts (CII).

With low viral load (< 50,000) for patients with CD4 cell numbers between 350 an 500/µl, and for all patients with CD4 cells above 500/µl, effects on surrogate markers are not as clear and a large body of expert opinion is reserved about recommending therapy when one considers the problems associated with long-term antiretroviral therapy (CIII)[11, 13].

Further Indications

Some HIV-infected patients develop a so-called acute retroviral syndrome immediately after the infection

Table 3. Indications for therapy and recommendation.

Clinical	CD4+lymphocytes/µl	HIV- RNA / ml (RT-PCR)	Therapeutic recommendation
HIV-associated symptoms and infections (CDC: C, B)	All values		AI
Asymptomatic patients (CDC: A)	< 200	All values	AI
	200-350	All values	BII
	350-500	>50,000- 100,000 copies	CII
		< 50, 000 copies	CIII
	>500	All values	CIII
Acute retroviral syndrome	All values	All values	CII, preferred in studies

which is closely followed or accompanied by seroconversion. It is characterised by constitutional symptoms, morbilliform exanthema, lymph node swellings and high HIV-RNA values. Data from long-term studies on antiretroviral combination therapy are not yet available for these patients. Studies on monotherapy with zidovudine have shown that the rate of early opportunistic infections can be lowered by a six month zidovudine monotherapy and that the CD4+ cell reduction can be limited [14]. However, a durable improvement in long-term prognosis from a time-restricted monotherapy could not be determined [15]. From experiences up until now, an early combination therapy starting before or during seroconversion can result in some patients in a recordable improvement in cell-mediated immune control of HIV according to immune functional tests. However, recent data (CROI 2004) have shown that clinical benefit and a significant improvement in surrogate parameters can not be achieved in this way during the first years of therapy [16, 17, 18]. Faced with the unclear long-term effects of such early therapy, treatment, as long as it is requested by a sufficiently informed patient, should only be provided within the framework of clinical studies or standardised treatment programs in order to clarify this open question.

Initial Therapeutic Regimen

In addition to virus burden and stage of disease, other factors such as lifestyle, co-morbidity, and other co-administered therapies should also be considered when selecting the initial drug combination. A range of options are available to provide an effective initial therapy. These include:

- A combination of one, usually boosted, protease inhibitor (PI) with two nucleoside analogue reverse transcriptase inhibitors (NRTI)
- A combination of one non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) with two NRTIs
- A combination of three NRTIs

Some experts favour a primary use of four substances for patients at high risk of virological failure (CII). A reduction of medication number from four to three after an induction phase (induction/ maintenance therapy) also appears to be possible. However, therapeutic regimes consisting of all 3 classes of drugs have not been shown to be superior for long-term therapies [19, 20].

Combinations with Protease Inhibitors

The effectiveness of PI-combinations has clearly been verified in patients with a very advanced immune defect. The effectiveness of combinations with boosted protease inhibitors is higher than with unboosted substances, and the risk of resistance development is lower [21].

Disadvantages of the currently available PIs include their unfavourable pharmacokinetics, a fact which demands the consumption of a large number of tablets over short time periods (although this can be ameliorated especially by PI boosting), as well as adverse effects and drug interactions. Metabolic disorders such as lipodystrophy, insulin resistance and diabetes are more frequently observed with PI combinations than with other combinations.

The inhibition of cytochrome p450 isoenzyme 3A4 (CYP3A4) (usually by application of a low dose of ritonavir, so-called boosting) clearly improves the pharmacokinetics of most protease inhibitors and makes it possible to provide a twice daily or even once daily therapy [22, 23, 24].

Combinations with NNRTIs

For NNRTIs in a triple combination therapy, data exist from two comparative studies with efavirenz +2 NRTI versus an unboosted protease inhibitor +2 NRTI over a duration of 48 weeks. In the direct comparison the combination with efavirenz was superior to that with indinavir concerning the proportion of patients with undetectable HIV-RNA in plasma, while in the second study the median time until failure of the first-used combination was clearly longer with efavirenz [25, 26]. In several other randomised studies with application of efavirenz, very high rates of virus suppression were shown also over a period of two

Table 4. Basis combinations and combination partners for the initial therapy (x).

Recommended combinations	**Nucleoside analogs**			**Protease inhibitor or NNRTI or third NRTI**	
	Zidovudine + Lamivudine	A I	+	Lopinavir + Ritonavir	A II
	Zidovudine + Emtricitabine Tenofovir + Lamivudine or Emtricitabine Abacavir + Lamivudine or Emtricitabine	A II		Efavirenz Nevirapine && Saquinavir (HGC or SGC) + Ritonavir FosAmprenavir + Ritonavir Indinavir + Ritonavir #	
	Stavudine + Lamivudine or Emtricitabine Didanosine + Lamivudine or Emtricitabine	B II			
	Zidovudine + Didanosine	C I&		Nelfinavir	B II
	Zidovudine + Zalcitabin Stavudine + Didanosine	D I& D II&		Indinavir Saquinavir SGC Amprenavir Atazanavir Delavirdine Ritonavir	C I/II*& C II** C II** C III (x) D II*** D I/II*&
	Zidovudine + Lamivudine		+	Abacavir	C II***
Rejected without question	2 NRTI §§ Combination of three nucleoside/tide-analogues without thymdine analogue §§		+	without combination partners	E I/II
	Combination without PI booster such as Ritonavir		+	Saquinavir HGC §§	E II
	Zidovudine + Stavudine §	E II	+	Every combination partner	
	Zalcitabine + Stavudine & Didanosine + Zalcitabine &	E III			
	Lamivudine + Emtricitabine §§	E III			

*Clinical end point study with indinavir and ritonavir (evidence class I) only for patients with CD4+ <200/µl, as well as with CD4<100/µl, otherwise evidence class II for both.

& Disadvantages regarding biocompatibility

&& Because of increased toxicity, nevirapine should only be employed reservedly in men with CD4 cell numbers >450/µl and in women with cell numbers >250/µl

Investigations on ritonavir/indinavir at a dosing of 100/800mg 2 x daily indicated a good virological efficacy, but high side effect rates due to nephrotoxicity. The first studies using low doses of ritonavir/indinavir 100/400mg, 2 x daily revealed a good virological efficacy with a clearly improved toxicity profile

**Disadvantage with dosage form (large number of tablets)

*** Little data on the therapy of patients with an advanced immune defect (CD4 < 100/mm3)

§ competitive phosphorylation

§§ rapid development of resistance

(x) Atazanavir is only authorized in Europe for the therapy of antiretrovirally pretreated patients. Only in the USA is there extended authorization for therapy naive patients. In therapeutic studies, unboosted atazanavir was in a virological sense comparably effective to nelfinavir and efavirenz [36]. Boosted Atazanavir like other boosted protease inhibitors appears more promising with regard to efficacy and resistance development. However, no data exist yet with this combination regarding therapy naive patients.

years. In these studies the combinations of efavirenz with lamivudine plus either zidovudine, or stavudine or tenofovir were identified as being particularly effective.

Regarding the combination of two nucleoside analogues and nevirapine in the initial therapy, data from one controlled study are available showing that the use of this combination produces similar results to those achieved with 2 NRTIs and indinavir [27].

In a direct comparative study of the two substances efavirenz and nevirapine, a comparable efficacy was shown [28].

Advantages of the NNRTI combinations include the easy dosage and smaller number of tablets (nevirapine is given twice daily as a tablet, and efavirenz once daily as a tablet) as well as the better pharmacokinetics. Efavirenz and nevirapine are metabolized via the cytochrome p450 system as well, so that interactions may occur with other medications.

In the case of planned changes of therapy or treatment interruptions, the long half-life of the NNRTI (levels can still be detected two weeks after cessation) and the enzyme induction they cause should be considered. For cessation of an NNRTI-containing combination, either of the two following strategies should be employed to reduce the risk of resistance development:1) with treatment interruptions that can be planned longer in advance the NNRTI can be initially replaced with a protease inhibitor. After approx. 2 weeks the therapy can then be interrupted by simultaneous cessation of all medications. 2) after removal of the NNRTI the remaining medications should be given for another seven days (BII/III) [29].

The risk of a resistance development is particularly high with more frequent interruptions of medication combinations containing drugs with differing half-lives [30].

Combinations of Three Nucleoside Analogues

Regarding therapies with combinations of three nucleoside/-tide inhibitors there are several studies over periods of 48 weeks (Trizivir - zidovudine+lamivudine+ abacavir) [31, 32]. The long-term data especially in patients with high plasma viraemia (HIV-RNA-copy/ml >100.000) suggest a lower activity compared to combinations of drugs from two substance classes. With the combinations tenofovir, lamivudine and abacavir as well as tenofovir, lamivudine and didanosine a surprising low efficacy was found that was not expected considering the synergy observed in-vitro [33, 34]. Also, for other triple-nucleoside analogue combinations the rates of complete inhibition of viral replication are not comparable to other multi-class regimes [27, 35].

The advantages of 3-fold NRTI combination are the simple dosing (e.g. one capsule twice daily) and the lower rates of interactions with other therapeutic agents (e.g. tuberculostatics) .

Under certain circumstances some experts consider the use of Trizivir as the initial therapy, especially in patients with a low level of HIV-RNA and a high risk of interaction with other required medications. If a triple nucleoside/nucleotide analogue is used initially, it should include a thymidine analogue to prevent the rapid development of resistance. Overall, a combination of nucleoside analogues should only be recommended in the initial therapy if a PI- or NNRTI-containing therapy is not feasible.

Summarising Evaluation

Among the various possible initial combinations, combinations of two nucleoside analogues + one NNRTI or a boosted protease inhibitor have proven to be particularly effective. The various combinations differ with regard to their spectrum of side effects.

The concept of boosting plasma levels of protease inhibitors by application of ritonavir at sub-therapeutic doses ("a baby dose„) is now established in everyday clinical routine and has also been taken into account in drug approvals. The addition of ritonavir to (fos)amprenavir, atazanavir, saquinavir and indinavir leads to an increase in nadir concentrations (minimum plasma concentration during the dosing pause) and a prolongation of the half-life with a moderate or minor increase in the maximally achieved concentration (peak level) [37].

Regarding nucleoside analogue-free combinations, the first data on the efficacy of double-PI-combinations and combinations of PI + NNRTI are now available [38, 39, 25]. The long-term efficacy and compatibility of such combinations has not yet been definitively clarified.

Patient Surveillance, Therapeutic Monitoring, Therapeutic Success and Failure

The most important laboratory parameters for surveillance of an HIV-infection include the quantitative measurement of CD4+-lymphocytes and HIV-RNA. They should be determined at the time-point of diagnosis and then at intervals of approx. 2-3 months, and HIV-RNA should always be determined with the most sensitive available test. Introduction of therapy and its further adaptations are indications for more frequent measurements.

For a patient on therapy whose HIV-RNA values are below the detection limit (currently 20-50 genome copies/ml), the viral load should be controlled approx. every 2-3 months. A significant change in virus replication can be assumed from a change of 0.5-0.7 log10 (corresponding to changes by factors of 3 to 6), while significant changes in CD4 values can be assumed with a decrease of 30 % or more in absolute values or around 3 % in relative values. Measurements that trigger the re-evaluation of therapy should be controlled by further blood sampling at shorter intervals. As a rule, however, measurements need not be made at intervals of less than 4 weeks.

Therapeutic Success and Failure

A decrease in HIV-replication to below the detection limit is considered as a therapeutic success. Therapeutic success can be evaluated at the earliest 4 weeks after the initiation of therapy or changes in therapy; often, however, three months and in some cases even 6

months must elapse before this can be done. Therefore a smaller decrease in HIV-RNA by 1 log10 after 4 weeks or the absence of a decrease to below the detection limit within a maximum of 6 months represents an inadequate therapeutic success and should prompt re-evaluation of the therapeutic regimen.

An inadequate therapeutic success or a therapeutic failure may be due to reduced absorption or increased metabolism of the active substances, drug interactions, pre-existing or selected resistance and/or an insufficient therapeutic compliance of the patient.

A relevant reduction in efficacy probably occurs when the HIV-RNA increases above the nadir of the decrease; a secondary therapeutic failure can be assumed if the HIV-RNA increases to a value that lays 1 log10 or less below the initial value.

In case of confirmed low-level reoccurrence of viral load (up to approx. 1,000 HIV-RNA copies/ml), the therapy should be re-evaluated and eventually intensified or modified as soon as possible.

Signs of an inadequate efficacy also include a poor increase/significant reduction in CD4+-lymphocytes, (see above) as well as further clinical progression. The evaluation of therapeutic failure according to the last criterion is often particularly hard to make. An antiretroviral therapy can be virologically effective, but the immune system may already be so heavily damaged, that an opportunistic infection might still occur.

Conversely, the immune reconstitution associated with the antiretroviral therapy may lead to an exacerbation of latent/overt infections (a so-called immune reconstitution syndrome), especially after a rapid increase in CD4+ values starting from a low starting value. This might demand the application of steroid hormones or even a postponing of the antiretroviral treatment.

Resistance Testing

Resistance of HIV against antiretroviral substances was already demonstrated early on after the first medications became available [40], as were the effects of resistance on the clinical course of an HIV-infection [41]. Furthermore, numerous retrospective studies exist for modern combination therapies, which have confirmed an association between development of resistance and therapeutic failure [42]. The results of randomised, prospective studies have been published over the last years which for the most part have shown a better therapeutic response for patients who were treated accordingly to their resistance status [43-49]. This led to the implementation of European and international guidelines for resistance testing in antiretroviral therapy [50, 51].

Resistance testing is necessary for therapeutic decisions after initial or multiple therapeutic failures. In such cases resistance testing should be carried out as long as therapy is still ongoing. Before initiation of therapy, in particular with a recently occurring infection, testing is recommended upon suspicion of infec-

Table 5. Summary of recommendations for resistance testing (for HIV-therapy in pregnancy and with HIV-infected children the specific recommendations of specialist societies are referred to).

	Recommendation	**Therapeutic recommendation**	**Comments**
Treatment naive patients			
Primary/ recent infection	Resistance testing recommended, when an antiretroviral therapy is begun	A II	Archiving of a plasma-sample recommended even if no antiretroviral therapy is introduced; Notification to the seroconversion register of the RKI *
Chronic infection, before onset of therapy	Resistance testing recommended	B III	Archiving of a plasma-sample which should be taken as soon as possible after the infection date
Treated patients			
After the first therapeutic failure	Resistance testing generally recommended before therapeutic switching	A II	Clarification of other causes of therapeutic failure is obligatory
With more extensive antiretroviral treatment beforehand	Resistance testing** generally recommended before therapeutic switching	A II	Clarification of other causes of therapeutic failure obligatory
In or after a therapeutic pause	Resistance testing currently only recommended within the framework of scientific studies	D III	Determination of reversion to the wild type*

see also: http://www.rki.de/INFEKT/AIDS_STD/SERO/KONVERT.HTM
** frequently, additional phenotypic testing is necessary

tion by a resistant virus. Epidemiological studies on the transmission of resistant viruses in newly infected patients have shown an 11% prevalence of primary resistance. As such, it is certainly justifiable to undertake a general resistance testing before an initial therapy is started (AII/BIII) [52, 53 ,54, 55, 56].

Genotypic and phenotypic HIV resistance tests are complementary regarding their approach and informative value. While phenotypic tests directly measure the sensitivity of a virus, resistance-associated mutations are verified by genotype testing. Genotypic testing is frequently sufficient for therapeutic decisions. An adequate interpretation of genotypic resistance findings should be performed with the best available interpretation aids and also considering any previous therapy-failures. Additional phenotypic testing is recommended, however, especially with the application of a more complex salvage regime and newer antiretroviral agents.

Determination of Therapeutic Drug Levels

Several studies have confirmed a correlation between the plasma concentration of protease inhibitors and their antiviral effectiveness [57, 58]. Although the benefits of therapeutic drug monitoring have not yet been assessed completely, measurement of plasma levels may be helpful in certain clinical situations. [59-61]. Plasma level measurements in combination with genotypic resistance testing usually suffice to explain an unsatisfactory therapeutic success.

Every decision on dose modifications must take into account the high intra-individual variability of plasma levels at different time-points due to dietary effects, disease stage and compliance.

An indication for therapeutic drug monitoring depends on the clinical-pharmacological properties of the antiretroviral medications applied:

NRTIs have to be transformed intracellularly into their active form by phosphorylation. No clear relationship exists between effect and plasma level. In this case it makes no sense to determine levels of these substances in plasma or serum. Assays that can determine intracellular triphosphate levels are currently being developed and evaluated [62].

Protease inhibitors are subject to considerable inter- and intraindividual variability regarding their gastrointestinal absorption and hepatic metabolism. Their degradation can be inhibited or induced by other pharmaceuticals and conversely these drugs may influence the metabolism of an eventually accompanying medication. As a result complex interactions are possible.

NNRTIs are better and more uniformly absorbed gastrointestinally than are PIs. Interactions during metabolic degradation also play a considerable role.

Overall, measurement of plasma drug levels should be carried out in the following therapeutic situations:

- Administering complex combinations of NNRTI/PI substances and accompanying medications that are expected to lead to interactions
- Lack of efficacy of an active principle or a combination of active principles
- Suspected malabsorption
- Occurrence of toxic effects
- Restricted liver function.

For evaluating effectiveness, the nadir level is the most important parameter, while for estimating toxic potential the entire pharmacokinetic course must be considered.

In earlier versions of these treatment guidelines the most important interactions of antiretroviral medicines were expressed in tabular form (formerly Table 6). Most interactions were examined in a two way mode, i.e. the interactions were tested only between two substances. This approach does not reflect the current reality, since patients are now usually taking more than two drugs concurrently. Because of the increasing number of available antiretroviral substances, the increasing number of medications used for side effect management, and the increasing body of data regarding interactions also with foods and legal/illegal recreational drugs, knowledge regarding interactions has now reached a complexity and scope that defies any attempts of tabular representation, and it also makes it difficult to describe and make any precise predictions about the interactions that might occur on an individual basis. The high inter-individual variability and the multiple interactions between protease inhibitors and NNRTI underscore the clinical importance of therapeutic drug-monitoring with antiretroviral combinations.

Various internet-based interaction databases and tools exist (e.g. **www.hiv-druginteractions.org**, **www.ifi-interactions-hotline.de**) that can provide assistance for estimating the potential for interactions with combinations and co-medications. One can also refer here to the comprehensive interaction tables published in the US-American therapeutic guidelines (e.g. under http://aidsinfo.nih.gov/guidelines/).

Apart from consideration of dosing and interaction information in the expert information provided by the pharmaceutical manufacturers, it is also recommended to measure plasma levels and adapt dosing in case of unsatisfactory responses to an ART (possibly due to a reduction of plasma levels through interactions), medication associated side-effects (e.g. due to a boosting of plasma levels through interactions), or when substances are concomitantly used that are known to interact (e.g. with St. John's worth preparations where the therapy also contains PIs or NNRTIs).

Therapy Changes and Interruption

Changes in therapy may become necessary due to ineffectiveness and adverse effects. An unambiguous definition of antiretroviral therapy failure can not be provided at this point in time. A large body of experts consider a controlled re-increase in HIV-RNA from immeasurable to measurable levels as a failure, while the conservative definition considers a re-increase in the order of less than 1 log 10 below the starting value as a failure. The alternative regimen selected after a therapeutic failure should include as many active substances as possible as well as a new substance class. As a rule, selection of the new combination should there-

fore occur on the basis of resistance testing results. Decisions on second and alternative therapies in particular demand specialist knowledge and should only be made by experienced and informed physicians.

A switching of an effective therapy for patients with adverse effects is also of course possible. This is the only clinical situation for which replacement of only one drug can be recommended without resistance testing. If interruption of therapy is required, all substances must be simultaneously discontinued, as long as this is an NNRTI-free combination (BIII). When ceasing an NNRTI-containing combination, the long half-life of the NNRTI (levels remain detectable after cessation for up to two weeks) must be considered, as must be the enzyme induction it causes, in order to reduce the risk of resistance development. Two strategies can be taken for this purpose: 1) Where therapy interruption can be planned longer in advance the NNRTI can be replaced at first with a protease inhibitor; after approx. 2 weeks the therapy can then be interrupted by the simultaneous cessation of all medications; 2) After cessation of the NNRTI, the remaining medications should be given for another seven days (BII/III).

Therapy Interruption

Interruptions of therapy may become necessary in cases where long/short-term adverse effects or incompatibility reactions occur. The more frequently a therapy is interrupted, the greater is the risk of development of resistance, especially with combinations of drugs with different half-lives and with pre-existing resistance mutations. In this respect, therapeutic strategies with predefined short intervals between medication dosing and treatment interruption can currently not be recommended. They do not fulfil the benefits hoped for and entail the above-mentioned risks. The concept of CD4-cell number-controlled therapy interruption is still unclear regarding its effectiveness. The goal here is to avoid any irreversible and disfiguring fat distribution disorders amongst other side effects and to reduce treatment costs. It has not yet been proven in studies whether a lasting reduction of lipodystrophy can be achieved, and how large the risk of resistance development is.

Structured therapy interruptions (STIs) represent a relatively new concept for the temporary interruption of therapy. This concept was based on the observation that during the phase of immune reconstitution by the antiretroviral therapy, the cellular immune response towards opportunistic pathogens is measurably improved, but not the HIV-specific cellular immune response. This has been attributed to the "absence" of HIV antigen after the decrease in viraemia occurring under HAART. In order to achieve a natural re-exposure to HIV antigens, the concept of structured therapeutic interruptions with alternating phases of antiretroviral therapy and pauses was developed in order to achieve a natural auto-vaccination during the therapy-free periods. However, in chronic infection this concept has been proven to be ineffective in a large number of pilot and randomised studies, and can no longer be recommended [63-65].

Thanks to research over the last few years, it has now become clear that therapy interruptions need to be evaluated in different clinical settings and should also be evaluated differently with respect to diverging clinical objectives.

Currently, interruptions may be instituted:

1. After a decision to initiate therapy that was too early according to current knowledge
2. In the course of treatment of an acute HIV-infection during or immediately after seroconversion with the goal of improving the endogenous immune response
3. As an attempt to reverse or reduce resistance-mutations prior to a change in therapy amongst intensively pre-treated patients
4. For the strategic prevention of long-term adverse effects
5. In case of toxic adverse effects
6. Upon patient's request.

For all these situations the lengths of the pauses in antiretroviral therapy is chosen arbitrarily. The optimal duration of the off-treatment interval in these different scenarios has not yet been determined. The timepoint at which therapy should be resumed (i.e. the critical CD4 cell number or virus burden) is also unclear. Controlled studies examining whether interruptions of therapy lead to a more rapid development of resistance or more frequent clinical complications are currently being undertaken. A final appraisal is still not possible. Whenever possible, controlled studies or surveys should be performed in cases where interruptions of therapy are employed for points 2-4.

Regarding 1: No information on the benefits or disadvantages of interruptions of therapy exists for those patients for whom therapy was started too early according to current guidelines. The vast majority of these patients achieved a good virus suppression and normalisation of immune system parameters. However, many of these patients are worried about the potential long-term toxicity of the therapy. A decision in favour of continuing or interrupting therapy amongst patients of this group can currently only be made on an individual basis and without any clear evidence to favour one option over the other.

Regarding 2: Positive effects of interruptions of therapy have been observed until now particularly in small pilot studies amongst patients, who were treated very early on after an acute HIV infection. Here, especially with very early treatment (before the 60th day after exposure), evidence was found in some patients for an improved immunological control of HIV infection after several interruptions of therapy. The duration of the improved immunological control after cessation of the therapy is probably not longer-term. Whether the early treatment with or without additional STI can also have a longer-term benefit can not yet be evaluated at this point in time.

The majority of studies were carried out in patients with chronic HIV infection. In this group, which until now has been the largest to be treated in such a way, immunological or virological advantages are not to be

expected from therapy interruptions, although a reduction of toxicity and costs might be (see under 4). In one of the few larger prospective studies undertaken on this subject (SSIT), no immunological or virological advantage could be confirmed amongst chronically infected patients under STI, but a reduction in increased blood lipid values was registered. As an unwanted consequence of therapy interruption, development of resistance could be shown in some individuals [65, 30].

With a therapy interruption a rapid re-increase of the viral load, presumably also entailing an increased infectiousness, should be reckoned with as a rule. The patient must be informed about this. Therapy interruptions should not be applied to patients with a very advanced immune defect (CD4 nadir<200/µl) or an initially high viral load (>500,000 copies/ml) at the onset of therapy unless there are overriding reasons for doing this. In such cases, a rapid and lasting deterioration of immunological status should be reckoned with under STI.

Pregnancy, Children, PEP

Recommendations exist for the antiretroviral therapy of HIV-infected children [66]. German-Austrian recommendations have already been prepared for therapy during pregnancy and for post-exposure prophylaxis after HIV exposure, and for this reason these situations have not been dealt with here [67, 68].

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