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REVIEW ARTICLE

Treatment of HIV infection: Swedish recommendations 2009

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Abstract

On 4 previous occasions, in 2002, 2003, 2005 and 2007, the Swedish Medical Products Agency (Läkemedelsverket) and the Swedish Reference Group for Antiviral Therapy (RAV) have jointly published recommendations for the treatment of HIV infection. In November 2008, an expert group under the guidance of RAV once more revised the guidelines, of which this is a translation into English. The most important updates in the present guidelines include the following: (a) treatment initiation is now recommended at a CD4 cell count of approximately 350/μl; (b) new recommendations for first-line therapy: abacavir/lamivudine *or* tenofovir/emtricitabine in combination with efavirenz or a boosted protease inhibitor (PI/r); (c) an increased focus on reducing the use of antiretroviral drugs that may cause lipoatrophy; (d) an emphasis on quality assurance of HIV care through the use of InfCare HIV; (e) considerably altered recommendations for the initiation of antiretroviral therapy in children. All infants (<1 y) should start antiretroviral therapy, regardless of immune status. Also, *absolute* CD4+ cell counts, rather than percentage, may be used to guide treatment initiation in children above the age of 5 y.

Introduction

HIV infection is a major global problem. UNAIDS estimates that approximately 30–36 million people are currently infected with HIV, and approximately 3 million die annually as a result of infection. In total, over 30 million people have died since the first case of AIDS was diagnosed in 1981. Up until September 2008, approximately 8400 HIV-infected patients had been reported in Sweden. Of these, more than 2200 have since developed AIDS and somewhat more than 1900 have died. It is, however, probable that the actual number of people who have died of AIDS is higher. In November 2008, more than 4300 adult patients with HIV and approximately 120 children were monitored and/or treated at the Swedish infectious diseases and paediatrics clinics.

Increased access to antiretroviral drugs has dramatically improved the prognosis for people infected with HIV. The mortality in the Swedish HIV cohort during 2007 was 1%. However, the life expectancy is still shorter than that seen in the general population [1]. The first antiretroviral drug, zidovudine, was introduced in 1987. Twenty-three new drugs have since followed. The introduction of combination treatment, which has resulted in significantly better results and lower risk of resistance development, has been of crucial importance for the success of antiretroviral therapy. Combination therapy was introduced in 1996, and immediately resulted in decreased morbidity and mortality. However, it does not cure the infection. Thus, treatment is presently expected to be life-long. Hitherto, therapeutic as well as prophylactic vaccine trials have been largely

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unsuccessful. Presently it is unclear whether effective vaccines will be feasible.

InfCare HIV—The Swedish quality assurance registry

The aim of the InfCare HIV registry is to assure that the same high quality of care is given regardless of what clinic the patient is treated at, and irrespective of the route of transmission through which the HIV infection was acquired. As of January 2009, all clinics in Sweden that treat adult patients are participating. Most of these openly report their treatment results. This is an invaluable aid for the monitoring of treatment quality and the identification of putative problems, as well as for assessing compliance with treatment guidelines such as these. InfCare HIV is also used as a tool for decision-making and expert consultations at point of care.

New antiretroviral drugs

Darunavir (Prezista®)

The labelling now includes both treatment-naïve and experienced patients with varying extents of resistance. The recommended dose for treatment-experienced patients remains darunavir/ritonavir (r) 600/100 mg twice daily, while the dose for the treatment-naïve is 800/100 mg once daily (using the new 400 mg tablets). The extension of the indication is based on 2 randomized controlled trials; ARTEMIS, in which darunavir/r dosed once daily was non-inferior to lopinavir/r in treatment-naïve patients, and TITAN, where darunavir/r dosed twice daily was superior to lopinavir/r in patients with moderate protease inhibitor (PI) resistance [2,3]. Darunavir has also been approved for twice daily paediatric use.

Ritonavir (Norvir®)

In 2009, the capsule is expected to be replaced by a tablet that does not require refrigeration.

Etravirine (Intelence®)

Etravirine is a novel non-nucleoside reverse transcriptase inhibitor (NNRTI), approved for use in combination with a PI/r in patients with NNRTI resistance. Etravirine is effective in patients with low to moderate NNRTI resistance, including patients with the key K103N mutation selected by, and conferring resistance to, efavirenz. The approval is based on 2 studies with similar design (DUET 1 and 2) where etravirine was compared with placebo, both together with an optimized background regimen including darunavir/r [4,5]. The safety profile so far appears favourable. As with the other NNRTIs, rash may occur; this usually subsides without necessitating discontinuation of etravirine.

Raltegravir (Isentress®)

This is the first drug of a new class of antiretrovirals, the integrase inhibitors (II). Raltegravir was approved in the European Union (EU) in the spring of 2008, for use in treatment-experienced patients. The indication will soon be extended to the treatment-naïve. The additional effect of raltegravir, compared to placebo, in heavily pre-treated patients in the pivotal BENCHMRK 1 and 2 studies was impressive. In the STARTMRK study in treatment-naïve patients, the efficacy was comparable to efavirenz. No side effects profile characteristic of raltegravir has been identified, but due to limited experience, the risk of long term side effects cannot yet be fully evaluated. A distinct advantage of raltegravir over the available PIs and NNRTIs is a lower propensity for drug–drug interactions. The extent to which clinically significant resistance to raltegravir appears at treatment failure is still somewhat unclear; however, the barrier to resistance appears to be higher than that of efavirenz, nevirapine and the cytidine analogues lamivudine and emtricitabine, but clearly lower than that of PI/r. Even though raltegravir will soon be approved for first-line therapy, it is not primarily recommended in treatment-naïve patients due to the limited experience available, and the subsequent uncertainty about putative long term side effects.

Maraviroc (Celsentri®)

Maraviroc belongs to the new drug class CCR5 antagonists, and is therefore an entry inhibitor (EI). CCR5 antagonists differ from the other available antiretroviral drugs in that they bind to a host receptor rather than a viral protein. Maraviroc is approved for use in treatment-experienced patients without detectable CXCR4-tropic virus. This is based on the outcome of 2 studies with similar design (MOTIVATE 1 and 2) where maraviroc was compared to placebo in extensively pre-treated patients. The safety profile has so far been good. Prior to initiation of maraviroc treatment, viral co-receptor tropism must be determined with a sensitive and validated method. Presently this is done with a phenotypic assay (Trofile®, Monogram Sciences, USA). The sample, with at least 1000 HIV-RNA copies/ml, must be refrigerated and transported to California. Results should be available within a maximum of 4 weeks. The possibility of

using alternative methods, such as genotypic analysis of the V3-region, is presently being investigated by academic research groups. Maraviroc treatment was somewhat less effective than efavirenz when studied in treatment-naïve patients, and resistance emerged more frequently in patients failing therapy (MERIT 1 and 2). It is presently unclear whether an indication for treatment-naïve patients will be approved in the EU.

Tenofovir/emtricitabine/efavirenz (Atripla®)

These 3 drugs are now available co-formulated. The indication approved by the European Medicines Agency (EMEA) is limited to patients who have already achieved undetectable viraemia (below the limit of quantification of standard assays) and have never experienced treatment failure. It is recommended that Atripla be taken fasting to lower the risk of adverse effects of efavirenz. This, however, leads to a somewhat lower exposure to tenofovir (it is otherwise recommended that tenofovir be taken with a meal). Uncertainty about the possibility of a submaximal efficacy of tenofovir is the reason for the limitation in the European indication.

Available drugs

The approved HIV-1 drugs that are presently available belong to 4 classes and comprise a total of 6 groups. The first class consists of 2 groups that inhibit reverse transcriptase (RT). These are the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). The second class consists of drugs that inhibit the viral protease and are called protease inhibitors (PI). The third class contains drugs that block the entry of the virus into the cell and are called entry inhibitors (EI). The entry inhibitors are divided into 2 subgroups: the fusion inhibitors and the CCR5 antagonists. Finally there is a fourth class – the integrase inhibitors (II), which block the virus-specific enzyme integrase, thus preventing the viral DNA from being integrated into the cellular DNA.

Starting treatment

Preparation for antiretroviral treatment

A prerequisite for successful treatment is a well-informed, motivated patient who is prepared to adhere strictly to the prescribed regimen. Since there is rarely an urgent need for immediate intervention, treatment should not be initiated until the patient has had the opportunity to thoroughly discuss his or her expectations and attitudes towards the disease and towards the proposed therapy. Optimally, this should take place on several occasions and should involve the treating physician and nurse, as well as other members of the team responsible for the treatment of the patient. Before treatment decisions are made, a risk assessment should be carried out to evaluate co-morbidities (e.g., cardiac, vascular, hepatic, psychiatric, substance abuse) that may be of importance for the tolerability and outcome of the treatment.

The patient should be provided with both verbal and written information about possible side effects of the proposed drugs, as well as concerning dosage intervals, dietary requirements, and other relevant treatment information. The need for maintaining a high level of adherence to the prescribed regimen must be stressed. When treatment is commenced, pill dispensers and other dosing aids may be of great value.

When should treatment be initiated?

There is general consensus that treatment should be initiated when the HIV infection causes symptoms, or is complicated by conditions brought on by immunological failure (Table I). Treatment is also recommended if specific HIV-related conditions appear, e.g. pronounced thrombocytopenia or central nervous system (CNS) symptoms. In the case of pregnancy or primary HIV infection, specific

Table I. Initiation of treatment.

Symptomatic HIV infection HIV-related conditions (see text)	Treatment is recommended irrespective of CD4 cell count
Asymptomatic HIV infection CD4 cell count approx. 350/μl	Treatment should be started as soon as the patient is sufficiently prepared, taking into account individual factors such as viral load, rate of CD4 cell decline, the CD4 cell percentage, age, co-infection with HBV or HCV, the psychosocial situation of the patient, and the patient's preferences and willingness to commence therapy

treatment decisions must be made. In patients with asymptomatic HIV infection, treatment decisions should be based on the CD4 cell count. It is recommended that treatment be initiated when the absolute CD4 cell count is around 350/μl (Table I).

There is a markedly increased risk of serious opportunistic infections when the CD4 cell count is <200/μl. Also in the interval from 200 to 350/μl there is an increased risk, though less pronounced, compared to >350/μl. There is probably also a somewhat increased risk of malignancies, as well as an increased rate of hepatic fibrosis progression in patients with hepatitis C co-infection. There have still been no randomized controlled trials to inform on the optimal timing of treatment initiation. Historically, opinions on when to start have varied, but presently there is a strong international trend towards starting treatment at higher CD4-cell counts (BHIVA (British HIV Association), EACS (European AIDS Clinical Society), IAS-USA (International AIDS Society-USA) guidelines). In the so-called SMART study (Strategies for Management of Antiretroviral Therapy), an increased all-cause mortality was seen in patients randomized to structured treatment interruptions. Some experts have interpreted this as indirect support for an earlier treatment initiation [6]. The presently recommended first-line treatment regimens carry a lower risk of adverse effects than did the previous generation; also the risk of virological failure and development of resistance is lower. The recommendation for when to start therefore reflects a weighing of the risk of HIV-related morbidity at different CD4 cell counts and the risk of treatment-related problems such as adverse effects, poor adherence, virological treatment failure and drug resistance.

Antiretroviral drug regimens in treatment-naïve patients

It is recommended that a first-line treatment in previously untreated patients comprise 2 NRTIs together with an NNRTI, or 2 NRTIs together with a PI/r (recommendation level A; evidence level 1b). The following regimens are recommended:

- Abacavir/lamivudine *or* tenofovir/emtricitabine in fixed dose combinations, together with efavirenz.
- If efavirenz is considered unsuitable (see below) it should be replaced by a PI/r.

Adding a fourth drug does not give any efficacy advantage, but increases the risk of adverse effects (evidence level 1b), and also the cost of treatment.

The choice of the first-line regimen (as well as possible subsequent regimens) should be made in dialogue and agreement with the patient, taking his/her particular situation into account. Here follows an account of the deliberations underlying the first-line recommendations, as well as particular considerations for specific patient groups.

The choice of NRTI

Two NRTIs are still recommended as part of the first-line regimen. One of these should be either lamivudine or emtricitabine. These drugs are considered equivalent in terms of efficacy and safety. As the second NRTI, abacavir (in co-formulation with lamivudine) or tenofovir (in co-formulation with emtricitabine) is recommended. Abacavir and tenofovir are considered equivalent, though with differing safety profiles. Abacavir should not be used in patients positive for HLA-B*5701 due to an increased risk of a hypersensitivity reaction. Tenofovir should not be used in patients with impaired renal function. Otherwise there is not sufficient evidence to clearly state whether there is an advantage of abacavir or tenofovir in terms of virological efficacy or risk of long term side effects. The Atripla® co-formulation is presently not recommended for treatment initiation, but patients who have reached virological control and have never experienced treatment failure may be switched to Atripla®.

Treatment with thymidine analogues (zidovudine, stavudine) (evidence level 1b) and didanosine (evidence level 5) should be avoided in treatment-naïve patients, since the risk of lipoatrophy and metabolic side effects are higher with these drugs. An exception to this rule is the use of zidovudine in pregnant patients, since this is well-documented and the duration of treatment is limited.

NRTI combinations that do not contain a cytidine analogue (lamivudine or emtricitabine) should not be used in treatment-naïve patients, due to a lack of any particular advantages, as well as a more limited evidence base [7].

The choice between abacavir and tenofovir

Concerning efficacy, comparative data on these 2 drugs had emerged between 2007, when the Swedish treatment guidelines were previously updated, and the expert group meeting in November 2008. In an investigator-initiated, double-blind trial ($n=1858$) performed in a US population, these treatment alternative were compared in treatment-naïve patients, in combination with either efavirenz or atazanavir/r. According to an interim analysis of the subgroup of patients with $>100{,}000$ HIV-RNA copies/ml in plasma, the time to virological failure was significantly shorter in patients treated with

abacavir/lamivudine, compared to tenofovir/emtricitabine [8]. At the time of the expert group meeting, no data on baseline resistance were available. In another, industry-sponsored, double-blind non-inferiority trial ($n = 688$) in treatment-naïve patients, abacavir/lamivudine was compared to tenofovir/emtricitabine, in combination with lopinavir/r once daily. Efficacy was similar, also in the subgroup of patients with a baseline viral load >100,000 copies/ml [9]. In a re-analysis of previous clinical trials with abacavir, a lower efficacy in patients with higher baseline viraemia could not be demonstrated [10].

In the Swedish guidelines of 2007, abacavir/lamivudine was recommended as the sole first-line NRTI combination. The only important toxicity that has definitely been ascribed to this combination is the abacavir hypersensitivity reaction. True hypersensitivity reactions almost exclusively occur in patients with the HLA-B*5701 genotype, and the problem can be avoided by testing for the presence of this allele prior to treatment initiation, which is recommended (see below) [11]. Patients who are positive for HLA-B*5701 should not receive abacavir [12].

By November 2008, 2 observational studies had emerged associating abacavir use with an increased risk of myocardial infarction and other cardiovascular events [13,14]. In both these non-randomized and somewhat overlapping cohorts, patients treated with abacavir had a higher underlying cardiovascular risk. This assumption was supported not only by estimation of known risk factors, but also by higher levels of circulating proinflammatory markers (that have been associated with cardiovascular disease) in abacavir-treated patients. When compiling data from randomized controlled trials, no tendency towards an increase in cardiovascular events could be seen [15]. The expert group considered the available evidence for a causal link between abacavir treatment and cardiovascular disease to be weak.

For tenofovir/emtricitabine, putative negative long-term effects on renal function and bone mass are a cause of concern, not least on the basis of preclinical data (Truvada® summary of product characteristics (SPC)). Though long-term follow-up of patients treated with tenofovir in clinical trials have not demonstrated evidence of significant toxicities, there is still some uncertainty about long-term renal and bone effects, particularly when co-treating with PI/r. When there is baseline renal impairment, treatment with tenofovir should be avoided.

The choice between NNRTI and PI

Efavirenz and lopinavir/r-based therapy in treatment-naïve patients was compared in an American trial (randomized, open-label) that mainly recruited homo-bisexual men. The efavirenz arm was shown to be superior in terms of total outcome as well as rate of virological failure [16]. On this basis, it is recommended that efavirenz be used for first-line treatment in all cases where this drug is not specifically considered unsuitable. Of note, however, emergent drug resistance in the event of virological failure is considerably more common with efavirenz treatment than with PI/r. This regards both NNRTI resistance (compared to PI resistance) as well as resistance to the NRTI components of the treatment regimen (particularly lamivudine/emtricitabine) [17]. The lower barrier to resistance of efavirenz compared to PI/r makes efavirenz a less suitable alternative when adherence is expected to be a problem. Furthermore, due to putative teratogenic effects, efavirenz is less suitable for women of child-bearing age in the absence of adequate contraceptive measures (Sustiva® SPC). Due to potential CNS side effects, efavirenz should also be avoided in patients with significant psychiatric disease, ongoing substance abuse or considerable mental instability. Finally, efavirenz lowers methadone exposure to a greater degree than do the PI/r that are recommended as alternatives for first-line therapy. Summing these considerations up, PI/r, rather than efavirenz, should be used in:

- Patients where erratic or low adherence, or treatment interruptions can be foreseen.
- Patients on methadone (see below).
- Patients with a history of significant psychiatric disease.
- Women of child-bearing age who do not take reliable contraceptive measures.
- Patients primarily infected with drug-resistant viral variants (see below).
- Women who have received, or are suspected to have received, nevirapine as prophylaxis against mother-to-child transmission.

The choice of NNRTI

Efavirenz is considered to have the more solid efficacy and safety documentation, not least vis-à-vis PIs, and is therefore preferred to nevirapine (recommendation level B). Nevirapine has been associated with severe liver injury and serious allergic reactions, including the Stevens–Johnson syndrome. Higher CD4 cell counts have been associated with an increased risk of such adverse events. Therefore nevirapine treatment should not be initiated if the CD4 cell count exceeds 250/μl in women or 400/μl in men [18]. In certain situations, however, nevirapine may be used instead of efavirenz. Efavirenz might be teratogenic and is therefore

contraindicated in pregnancy. Nevirapine may thus be preferable in pregnancy, and in patients wishing to become pregnant. Furthermore, in cases where the possibility of efavirenz-related CNS side effects is considered particularly problematic, nevirapine may be an option. However, in both of these situations, a PI/r is primarily recommended, rather than nevirapine. Etravirine has hitherto not been studied in treatment-naïve patients, and is therefore not recommended for this category.

The choice of PI

PIs should generally be ritonavir-boosted (PI/r), as these regimens are more efficacious, and the risk of drug resistance in the event of treatment failure is lower than for unboosted PIs [19]. Occasionally treatment with unboosted atazanavir may be mandated, if ritonavir is not tolerated due to adverse effects. This, however, presupposes that there is no drug resistance, that no acid-reducing agents are used (see below) and that the adherence of the patient is likely to be good.

- In treatment-naïve patients without drug resistance, the virological efficacy of atazanavir, darunavir, fosamprenavir, lopinavir and saquinavir is considered roughly equivalent.
- There is no scientific basis for generally recommending any of these agents over the others.
- In Sweden, atazanavir and lopinavir have been the most widely used PIs
- Indinavir and nelfinavir are not recommended, and tipranavir is not indicated for treatment-naïve patients.

Other drug combinations in first-line treatment

Triple NRTI combinations should not be used, since their virological efficacy is lower than that of the recommended regimens, and since combinations without a thymidine analogue (zidovudine and stavudine), which are associated with a high frequency of adverse events, are not virologically rational.

The 'NRTI-sparing' combination of efavirenz and lopinavir/r has demonstrated sufficient efficacy, but is associated with an increased frequency of metabolic side effects, and more drug resistance in the event of virological failure. However, this combination may be considered if the entire NRTI class is considered unsuitable [16].

The integrase inhibitor raltegravir has similar efficacy to efavirenz (non-inferiority) in first-line therapy, and will within a short time be approved for this indication. Since the cumulative experience of this drug class is still limited, raltegravir is not recommended for first-line treatment. Also, compared to efavirenz, it is not considered cost-effective in this situation. Raltegravir, however, should be considered in patients for whom the recommended first-line regimens may be unsuitable, for instance due to contraindications, intolerance and/or drug–drug interactions.

Cost-effectiveness

The relative cost-effectiveness of different antiretroviral regimens has not been addressed in previous Swedish guidelines. Notably, there are many treatment alternatives with roughly equivalent efficacy and tolerability in treatment-naïve patients. The cost of these different treatment alternatives, however, varies considerably. For instance, in Sweden in October 2008, using Truvada® (tenofovir/emtricitabine) was 50% more expensive than using Kivexa® (abacavir/lamivudine). Using one of the approved and recommended PI/r costs 57–86% more than did efavirenz. The expert group is of the opinion that cost-effectiveness should be considered in situations where there are several treatment alternatives that are, in general terms, clinically equivalent.

Patients primarily infected with drug-resistant virus

Primary infection with drug-resistant HIV-1 has, during the last few years, been demonstrated in somewhat less than 5% of cases in Sweden. In most of these patients, resistance has been limited to 1 or a few NRTI-resistance mutations. When treatment is initiated in such cases, it is important to keep in mind that further resistance mutations may have been transmitted, though the major virus population has reverted to wild-type. This mainly pertains to the M184V mutation conferring resistance to lamivudine/emtricitabine, and probably also to NNRTI resistance. For this reason, PI/r-based therapy should be considered for patients primarily infected with drug-resistant virus, even in cases where the detected drug resistance is limited; this since PI/r have a higher barrier to resistance than do NNRTIs. Resistance testing should be performed if the treatment response is not satisfactory.

Treatment goals and follow-up

The virological goal is a decrease of plasma HIV-RNA by at least 2 $\log_{10}$ copies/ml after 4 weeks, and to levels undetectable with routine methods within 3-4 months of treatment initiation (recommendation level B). If the initial viral load is very high, the time to undetectable viraemia may be somewhat longer.

In a small fraction of patients, low level viraemia (40–150 copies/ml) will be detectable despite adequate treatment and adherence. This proportion may be somewhat larger with the latest method for routine HIV-RNA quantification (Cobas Taqman PCR) compared to the previous one (Roche Amplicor) (evidence level 5). Therefore, in some patients where the treatment regimen as well as adherence seem fully adequate, a detectable but low level (<150 copies/ml) of viraemia may be acceptable and not considered as treatment failure.

Cases where repeated measurements show a plasma viraemia >150 copies/ml despite at least 6 months of antiretroviral treatment, should be considered definite treatment failures.

Continued treatment

Switching therapy despite satisfactory clinical effect

Switching nucleoside analogues. Zidovudine and didanosine should only be used in the very limited number of patients where this is motivated due to the drug resistance pattern, whereas there are no reasons at all to use stavudine in Sweden today. Thus it is notable that, according to data from the InfCare HIV database, in November 2008, 24% of Swedish patients were using zidovudine, 5% didanosine and 1% stavudine.

It is well-known that the risk of lipoatrophy is greatly increased with use of stavudine or zidovudine. Data are lacking, but on a mechanistic basis this may also be suspected for didanosine. Lipoatrophy is often irreversible, which further exacerbates the consequent stigmatization and psychological burden of this condition. Presently, there are alternative treatment options available for the vast majority of patients treated with the culprit drugs. Therefore, the expert group strongly recommends that zidovudine, didanosine and/or stavudine be replaced by other, less toxic drugs in cases where an unavoidable rationale for their use is lacking.

Switch due to manifest adverse effects. Changes of the treatment regimen due to side effects should preferably be done by substituting a drug in the same category, with a different adverse effects profile, for the drug presumed to cause the side effects. An NNRTI may also be replaced by a PI/r, and vice versa.

Whenever a treatment regimen is changed, the previous treatment history, as well as drug resistance, must be considered. If the treatment history and/or resistance testing indicate resistance against 1 or several drugs, treatment simplification should not include those drugs, or drugs that are cross-resistant. The plasma HIV-RNA load should be monitored 1 month after the change of drug regimen. If the viral load remains below 50 copies/ml, the patient should undergo further testing 2 to 4 times annually (recommendation level C). For the management of altered body fat distribution, see below.

The management of treatment failure

The management of treatment failure requires individualized decisions and specific competence. In this context, treatment conferences with experienced HIV specialists, pharmacologist and virologist are of great value. The internet-based InfCare HIV database and decision-making tool is very helpful for real-time expert consultations at a distance. Its use is strongly encouraged, as prompt management of treatment failure is important.

Virological treatment failure (for definition see above, under "Treatment goals and follow-up") is associated with a progressive accumulation of resistance mutations and should be managed without delay. With low-grade viraemia, the risk of resistance development is greater in patients who have already acquired drug resistance [20]. The most common cause of virological failure is insufficient adherence to medication. The following points should be considered in a patient failing therapy:

- Adherence and the routines surrounding the intake of the antiviral drugs should be carefully assessed.
- All drug treatment, HIV medications as well as other drugs (including herbal remedies), should be assessed with an eye to putative drug–drug interactions. For instance, in Sweden all categories of acid-suppressing drugs may be purchased free of prescription, and co-administering such drugs with atazanavir may significantly decrease the uptake of the latter.
- Dietary habits and other possible reasons for decreased drug absorption should be discussed.
- Plasma drug concentrations should be measured, if the results may be expected to have impact on the further case management (see below).
- Genotypic resistance testing should be carried out, both in patients with first-time failure (recommendation level B), and in patients with multiple failures (recommendation level A) [21]. High-level resistance against efavirenz, nevirapine, lamivudine and emtricitabine occurs rapidly (within weeks) when treatment fails. Measurable levels of viraemia during treatment

with NNRTIs, lamivudine or emtricitabine (excepting the first phase of treatment), generally implies that resistance to these drugs has developed.

The choice of therapy after treatment failure is made on an individual basis, and is determined by treatment history, drug resistance patterns and the perceived causes of treatment failure, including putative adverse effects. The same treatment goals as in first-line therapy apply in patients with first-time failure, as well as after multiple failures.

The presence of at least 2 active drugs in the new treatment regimen considerably improves treatment outcome; for this reason treatment with at least 2 active drugs should always be aimed at [22,23]. A number of new drugs are now available for patients with extensive resistance to the older drug classes (NRTI, NNRTI, PI). These include the PI/r darunavir/r, the NNRTI etravirine, the integrase inhibitor raltegravir and the CCR5 inhibitor maraviroc (if X4 tropic virus is not present). In clinical practice, lamivudine or emtricitabine is often retained in the regimen even though high-grade resistance is present; this since the signature mutation M184V decreases viral fitness. Thereby its maintenance confers a moderate indirect antiviral effect. However, the clinical value of this is unclear. Due to toxicity concerns, zidovudine, didanosine and stavudine should also, if possible, be avoided in patients with advanced drug resistance [24].

Drug regimens for patients with extensive resistance should be tailored to the individual resistance pattern. Concerning recommendations for monitoring, see below.

Cessation of treatment

Structured treatment interruptions have been associated with negative clinical, immunological and virological effects, and have also been associated with an increased mortality (evidence level 1) [25]. Patients should be advised against discontinuing therapy of their own accord. If, despite this, a treatment interruption is necessitated for some reason, the risk of inducing drug resistance should be considered, since the half-life of the different drugs in a regimen may differ widely. This problem mainly pertains to the NNRTIs, and to lamivudine and emtricitabine. There are no evidence-based recommendations on how to handle this problem, but 1 month of lopinavir/r monotherapy following the discontinuation of an efavirenz- or nevirapine-based combination may be considered.

Careful information on the risks of treatment cessation, as well as continued medical support, is of great importance in this situation. It is also important to inform the patient of the increased risk of HIV transmission after a treatment interruption. Since precipitous declines in CD4 cell counts are common after treatment cessation, monitoring of CD4 levels 1 month after discontinuation, and then every other month, is recommended during the first 6 months. Plasma HIV-RNA should be monitored in accordance with the general recommendations.

Guidelines for monitoring

Drug adherence

The most important factor for successful antiretroviral therapy is adherence to the treatment regimen. This fact should be carefully discussed before the start of treatment. Adherence should be systematically assessed and documented at every patient visit [26,27].

InfCare HIV

Due to the large amount of information necessary for the assessment and monitoring of HIV-infected patients, treated or untreated, the use of InfCare HIV, an internet-based database, national quality registry and decision-making tool, is recommended. It includes a graphic presentation of the treatment history of the patient, featuring items such as drugs prescribed, HIV-RNA levels and CD4+ T-cell counts. InfCare HIV greatly facilitates consultations at a distance. The program is also a valuable tool in meetings with the patient, where the discussion of present or future treatment is made easier. The system now covers virtually all Swedish HIV patients. The expert group strongly recommends that all Swedish clinics treating HIV patients should participate in the national InfCare HIV quality registry, and that treatment results at each centre be made public.

Laboratory monitoring

The recommended routine laboratory monitoring is summarized in Table II. When a treatment is stable and functioning well, monitoring twice yearly is sufficient, while more frequent monitoring may be mandated in cases of problems with, e.g., drug resistance or adherence. Resistance testing is recommended at the time of HIV diagnosis and in the case of treatment failure (evidence level 2b, recommendation level B).

Table II. General laboratory monitoring.

New patients	Weight+height+blood pressure
	HIV-RNA, resistance test, CD4+ cells
	Full blood count
	S-creatinine, Na, K, albumin
	S-bilirubin, AST, ALT, GT, ALP, LD
	Fasting blood glucose
	S-cholesterol, including HDL, LDL
	S-triglycerides
	Syphilis serology
	Hepatitis serologies (A+B+C)
	STI screening offered to all patients
	U-albumin, U-erythrocytes, U-glucose
	Referral to gynaecologist (women)
Untreated patients	Weight+blood pressure
	HIV-RNA, CD4+ cells
	Full blood count
	S-creatinine
	S-ALT, GT
Patients on antiretroviral therapy	Weight+blood pressure
	HIV-RNA, CD4+ cells
	Full blood count
	S-creatinine
	S-ALT, GT, bilirubin
	S-cholesterol,[a] including HDL, LDL
	S-triglycerides[a]
If treated with tenofovir,[b] also	Urinary dipstick
	S-K
	S-phosphate

S-, serum; U-, urinary; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GT, glutamyl transferase; ALP, alkaline phosphatase; LD, lactate dehydrogenase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; STI, sexually transmitted infection.

[a]Lipids should be monitored during the first year of therapy. Thereafter they should only be monitored if abnormal values have been found, or if treatment is altered.

[b]If tubular injury is suspected, U-protein HC (= a_1-microglobulin) and U-electrophoresis may add further information.

Patients with stable, well-functioning treatment regimens may have their scheduled appointments with a nurse specializing in HIV care, rather than with a doctor.

Determination of CD4 cell counts and T-cells

CD4 cell counts should be determined by means of flow cytometry, employing recommended, quality-controlled methods. The CD4 cell count is used as a measure of the degree of immune deficiency, and is the most important prognostic marker for the risk of opportunistic infections. For this reason, the CD4 cell count is used to decide when antiretroviral therapy is indicated. Furthermore, the CD4 cell count is used as a complement to plasma HIV-RNA measurements, to monitor the effect of antiretroviral treatment. The absolute CD4 cell count, as well as the CD4 cell percentage (of total T-lymphocytes), are relevant for the assessment of immune deficiency and treatment effect.

Measurement of plasma HIV-RNA

Plasma HIV-RNA is the most important indicator of the effectiveness of HIV treatment. In untreated patients it provides an indication of disease activity, and gives an idea of how rapidly CD4 cell counts may be expected to decrease (evidence level 2a). Several commercial kits are available for HIV-RNA quantification. Ideally, all genetic subtypes should be measurable. Differences in measured HIV-RNA levels >0.5 $\log_{10}$ (approximately a 3-fold increase or decrease) should be considered to represent true variations (evidence level 2a). Most available assays do not work for quantification of HIV-1 group N and O, and HIV-2. These variants can be quantified on demand, at The Swedish Institute for Infectious Disease Control (SMI, Smittskyddsinstitutet).

It is possible to measure HIV-RNA in other compartments than plasma, such as liquor or semen, but this is rarely of importance. Presently, quantitation of HIV-DNA has no role in routine HIV care.

Testing for drug resistance

Resistance testing is used to guide the choice of antiretroviral therapy, in order to maximize the likelihood of a satisfactory virological response. The results should be evaluated in consultation with an experienced clinician, and preferably also with a clinical virologist. The virologist consultation may take place through InfCare HIV. Routine genotypic resistance testing identifies mutations in the protease (PR) and reverse transcriptase (RT) genes, through sequencing of viral RNA obtained from plasma. In addition to PR and RT, assays for analysis of the envelope (*ENV*) gene (in enfuvirtide treatment) and the integrase gene (in raltegravir treatment), are available on request. The inference of viral drug resistance is based on an evaluation of the mutations found in these genes. Mutations in PR are categorized as primary or secondary. There are websites and consensus documents from expert groups in Europe and the USA that can be used as guidelines for the interpretation of test results (e.g., http://hivdb.Stanford.edu and http://www.medpocket.com). The laboratory should provide an interpretation of the mutation pattern found, and also the possibility for the clinician to discuss the interpretation, since this has

been demonstrated to improve treatment outcomes (evidence level 2a, recommendation level B).

EuResist is a bioinformatics tool available free of charge at http://engine.euresist.org. The user enters clinical data and the viral sequences of a given patient, and the program returns the 10 drug combination regimens calculated to have the highest probability of success, given the resistance pattern. Comparative analysis has shown that the EuResist method has a higher predictive accuracy than does the Stanford Drug Resistance Database or clinical experts (evidence level 2a). A drawback of EuResist, however, is that new antiretroviral drugs are introduced to the system with a certain lag-time, since companies have responded negatively to requests for pre-marketing drug resistance data.

Resistance testing can be performed retrospectively on stored, frozen samples. Sometimes it is of value to re-analyse old resistance data using updated algorithms for interpretation. This is particularly the case when considering treatment with the newer PIs.

It is important that sampling for resistance testing is done when treatment is ongoing, since resistance mutations may not be detectable in plasma if treatment is discontinued or changed (evidence level 2b). This phenomenon is known as reversion. Plasma samples with less than 500–1000 HIV-RNA copies/ml are often difficult to analyse. In these cases, sequencing of cellular HIV-DNA may be considered. Viral variants represented in less than 20–50% of the virus population (minor variants) will not be detected with routine methods (evidence level 1b).

Phenotypic resistance testing is presently not routinely used in Sweden. This method of testing determines the drug concentration necessary to inhibit the in vitro viral replication by 50% of maximal (IC_{50}).

Management of important adverse effects of antiretroviral therapy

Altered distribution of body fat

A major side effect of the thymidine analogues zidovudine and stavudine is the loss of subcutaneous fat, primarily about the face, extremities, and gluteal region (lipoatrophy) (evidence level 1). This effect is mainly attributed to the mitochondrial toxicity of the thymidine analogues. Since didanosine also exhibits pronounced mitochondrial toxicity in vitro, and is associated with an increased risk of lactic acidosis (considered to be a clinical manifestation of mitochondrial toxicity) [28], it seems likely that didanosine could also cause lipoatrophy, though this has been insufficiently investigated. There is no evidence that any drugs other than NRTIs cause lipoatrophy. Switching away from stavudine and zidovudine, and perhaps also didanosine, may cause some reconstitution of subcutaneous fat. The extent of this varies between individuals, and is sometimes not clinically apparent.

The loss of fat, particularly in the face, can be stigmatizing, whereas the loss of fat in the gluteal region and in the soles of the feet may be painful. The presently available treatment for facial fat loss is repeated injections of fat substitute. Lipoatrophy in the sole of the foot can be treated with gel-cushions in the shoes. There is no satisfactory treatment available for lipoatrophy in the gluteal region. Injection of fat substitute should be performed by a specialist in cosmetic surgery, or by a physician with a similar expertise.

Fat accumulation in around the neck, breasts and/or abdominal region (lipohypertrophy) has been associated with PI treatment. In a typical case of lipohypertrophy, the accumulation of fat emerges after about 6 months of therapy, and then remains relatively stable. The effect of switching from a PI to an alternative agent in cases of noticeable fat accumulation has not been thoroughly evaluated. In small published series, suction-assisted lipectomy has been used successfully to treat lipohypertrophy in the back of the neck ('buffalo hump') [29].

Metabolic disorders

The major causes of metabolic disorders and increased cardiovascular risk in HIV-infected patients are the same as those seen in persons who are not HIV-infected, such as smoking, dietary habits, lack of exercise and heredity. In addition, antiretroviral therapy – primarily PI (unboosted atazanavir being an exception), stavudine and to some extent zidovudine – is associated with metabolic disorders (evidence level 2a). Hyperlipidaemia with increased triglycerides, increased total cholesterol and low density lipoprotein (LDL)-cholesterol is common, as is insulin resistance, sometimes resulting in manifest type 2 diabetes. Treatment with PIs has been associated with an increased risk of myocardial infarction in a large cohort study (DAD; Data Collection on Adverse Events of Anti-HIV Drugs) [30]. The benefit of antiretroviral therapy, however, greatly exceeds any increased cardiovascular risk due to metabolic side effects.

Metabolic disturbances such as increased LDL-cholesterol and hypertriglyceridaemia are usually reversible on discontinuation of therapy. Clinical trials have also demonstrated improved lipid values after switching to atazanavir-, abacavir-, tenofovir- or NNRTI-based regimens [31–33].

In case of hyperlipidaemia the total cardiovascular risk should be evaluated according to practice guidelines. Total cholesterol <5.0 mmol/l and LDL-cholesterol <3.0 mmol/l is usually considered to be desirable; these parameters, though, should be co-evaluated with other factors of importance for cardiovascular risk (e.g., age, heredity, smoking habits, blood pressure, triglyceride levels). Increased cholesterol levels with low high-density lipoprotein (HDL)-cholesterol, however, poses more of a risk than does isolated hypertriglyceridaemia. Smoking cessation is always recommended, and particularly so if blood lipids are elevated. The patient should be given dietary advice and exercise guidance. Referral to a nutritionist may be considered. If possible, drugs that are associated with metabolic side effects should be replaced by drugs that are not.

If the effect of these measures is not satisfactory, the use of lipid lowering drugs should be considered, in accordance with general practice guidelines for patients not infected with HIV. The risk of drug–drug interactions, however, should be considered. When co-treating with PIs and some statins, there is a risk of elevated statin concentrations, which may increase the risk of statin myopathy (see below) [34,35]. Therefore one should carefully follow the recommendations in the prescribing information for the respective drugs when co-treating with PIs and statins. Co-treating with statins and other presently available antiretrovirals does not pose any particular drug interaction problem.

Patients who have or develop diabetes mellitus should be managed according to practice guidelines for this disease, and the antiretroviral treatment should be adjusted as for hyperlipidaemia.

Lactic acidosis

This is a rare but life-threatening condition that is primarily associated with stavudine treatment, and with the drug combinations stavudine+didanosine and didanosine+ribavirin [36,37]. The present-day risk of drug-induced lactic acidosis in HIV patients ought, therefore, to be extremely low, as the agents responsible for this should rarely, if at all, be used.

Hepatotoxicity

In HIV-infected patients with latent chronic liver disease, elevated liver enzymes are common following the initiation of antiretroviral therapy [38]. In most of these patients, the liver enzyme elevation is moderate, and often reverts to baseline even though the antiretroviral therapy is continued. In patients with liver injury due to chronic hepatitis, however, the risk of serious hepatic adverse events is also elevated. These patients should be monitored closely following the initiation of antiretroviral therapy. When choosing antiretroviral agents, drugs that have been associated with severe hepatic adverse effects should be avoided. Today this particularly pertains to nevirapine [18] and tipranavir (Aptivus® SPC) (recommendation level B).

Further guidance concerning the proper maintenance dose of PI/r in patients with moderately to severely compromised liver function, can be obtained by analysing plasma drug concentrations. For patients with severe hepatic dysfunction (Child–Pugh B and C) the documentation for the safe use of PI/r and NNRTI is incomplete. Nevirapine and tipranavir are contraindicated, but other drugs should also be used with great caution. If a serious liver reaction occurs, discontinuation of the antiretroviral therapy should be considered. If possible, a different combination of drugs should be used when antiretroviral therapy is restarted.

Renal toxicity

There are a number of cases published in which tenofovir-treated patients have developed proximal tubular dysfunction and the Fanconi syndrome [39]. It appears that this may be more common when a PI/r is part of the treatment regimen, which could be due to the approximately 30% increase in tenofovir exposure seen in this situation. Some observational studies have also implied an increased frequency of subclinical renal impairment in patients treated with tenofovir, compared to patients treated with other NRTIs [40]. However, clinical manifestations of the tenofovir effects on renal tubuli have been distinctly rare in the major clinical trials cohorts [41]. Still, tenofovir should be avoided in patients with impaired renal function (glomerular filtration rate <50 ml/min).

There is no need for dose adjustments of PIs and NNRTIs in the presence of impaired renal function. Dose adjustments are recommended for the NRTIs (excepting abacavir). Further information on this is found in the SPC for the respective agents.

Hypersensitivity reactions

Hypersensitivity and/or exanthema may occur during treatment with any antiretroviral drug. The most serious cases have been reported in connection with the use of nevirapine and abacavir (evidence level 4).

Approximately 5% of unselected patients initiating abacavir treatment develop a hypersensitivity reaction (HSR), usually manifesting as fever with

rash and/or other symptoms. This is sometimes severe (for details, see Ziagen® SPC). Continued abacavir treatment in this situation, or reinstatement of abacavir treatment in someone who has discontinued due to hypersensitivity, may be lethal. The presence of the HLA class 1 allele HLA-B*5701 is highly associated with the risk of HSR. Conversely, true HSR very rarely occurs in patients lacking this allele [42,43]. HLA-B*5701 is present at different allele frequencies in different populations. Genotyping for HLA-B*5701 is recommended prior to initiation of abacavir therapy (recommendation level A). In patients who are positive for HLA-B*5701 the use of abacavir is contraindicated, as the positive predictive value for HSR is approximately 60% [12]. The safety of abacavir rechallenge in patients with a history of clinical HSR, who are later tested as HLA-B*5701 negative, has not been systematically evaluated.

A common side effect of nevirapine is skin rash, which has been reported in approximately 15% of treated patients. It usually appears in the early stages of treatment, sometimes accompanied by a general feeling of illness, fever, joint and muscle pain, lymphadenopathy, and hepato-nephrotoxicity (evidence level 4). Since severe skin reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis may occur, discontinuation of nevirapine should be considered in the event of any skin rash (recommendation level C). In the case of mild or isolated skin rashes, the patient should remain in close contact with the treatment centre. Efavirenz and etravirine have also been associated with a relatively high frequency of rash, although usually of mild to moderate severity.

Treatment in special situations

Antiretroviral treatment in children and adolescents

More than 90% of all children with HIV have been infected through vertical transmission during the last part of pregnancy, during delivery or through breastfeeding. In Sweden, since 1999 only 1 infant whose mother was known to be infected before delivery has been vertically infected. This is due to a high coverage HIV screening of pregnant women, as well as to efficient and generally available prophylaxis against mother-to-child transmission [44]. However, every year HIV infection is diagnosed in several children who have migrated from regions of high HIV prevalence. Presently, approximately 120–130 children and adolescents below the age of 18 y, with a known diagnosis of HIV, are living in Sweden.

Initiation of antiretroviral treatment

As in adults, adherence to treatment is crucial for success. The situation of the entire family of the child should be considered prior to treatment initiation.

To a certain extent, there are considerations in treating children and adolescents that are different than in the treatment of adults. An important difference between paediatric and adult HIV infection, is that perinatally infected children acquire HIV during a period when the immune system is immature. This causes a different immune response from that seen in adults. In perinatal infection, the immune system is not capable of reducing the initial high-level viraemia, which may persist for a long time – often up to the age of 5 y [45]. The normal range of absolute CD4 cell counts varies with age, and has, until recently, not been used for the evaluation of immune function in paediatric HIV infection until after puberty, when adult guidelines have been applied. The CD4 cell percentage (of the total lymphocyte count) is less age-dependent [46].

The recommendations for treatment initiation presented in this document differ in several ways from the previous guidelines (Table III). For infants (<1 y), it is now recommended that treatment be started regardless of immune status. This is due to emerging experiences of the efficacy of antiretroviral therapy in infants, as well as the difficulty in predicting disease progression (the risk of AIDS and death) in this population [47,48]. If treatment,

Table III. Initiation of antiretroviral therapy in children.

Infants 0–1 y	Treat all patients Treatment deferral and intense monitoring may be considered in asymptomatic infants with CD4+>30% and uncertainty about the feasibility of adequate adherence
Children 1–<3 y	Treat all children with CDC class B[a] or C disease Treat all children with CD4+<25% or 750×10^6 cells/l Closer monitoring if HIV-RNA >250,000 copies/ml
Children 3–<5 y	Treat all children with CDC class B[a] or C disease Treat all children with CD4+<20% or 500×10^6 cells/l Closer monitoring if HIV-RNA >100,000 copies/ml
Children and adolescents ≥5 y	Treat all with CDC class B[a] or C disease Treat all with CD4+<350×10^6 cells/l

CDC, Centers for Disease Control and Prevention.
[a]The CDC class B conditions 'Single episode of serious bacterial infection' and 'Lymphoid interstitial pneumonitis (LIP)' are less associated with an unfavourable prognosis than are other class B conditions, and do not always motivate the initiation of antiretroviral therapy.

despite this recommendation, is not initiated (e.g., due to a very high risk of poor adherence), the clinical status and laboratory parameters of the patient should be closely monitored.

It has recently been shown that similar criteria can be used to guide treatment initiation in children ≥ 5 y of age, as in adults [49]. For younger children the CD4 cell percentage is still used, since these values are less age-dependent (Table III).

Studies in adults have led to the recommendation of treatment initiation at higher CD4 cell counts than was previously the case. Data from paediatric trials imply that the immunological response to therapy is improved when treatment is started at an earlier age. Due to high baseline viral loads, however, the time to undetectable viraemia tends to be longer in young children, which may increase the risk of resistance development [50]. Also, adherence may be problematic, and particularly so in the asymptomatic child. The importance of adherence, and how this must be maintained, should be carefully discussed with parents/caretakers prior to treatment initiation.

There are differences between children and adults regarding the clinical progression and symptomatology of HIV infection. In paediatric HIV treatment, the clinical and immunological classification published by the Centers for Disease Control and Prevention (CDC) in 1994 is used [51] (Table IV). Both European and US treatment guidelines are available, as are guidelines from the World Health Organization (WHO). European and US guidelines have previously diverged on several points, but lately the viewpoints have largely converged.

Choice of the initial treatment regimen in children

Resistance testing should be performed prior to treatment initiation. If this is not possible, the treatment history and pattern of resistance of the mother should be considered, provided that such information is available.

The number of drugs approved for paediatric use is limited. The taste of the formulations and the tablet/capsule size is of greater importance than in adults. Paediatric dosing is governed by body weight or body surface area (a function of weight and height). Since children periodically display rapid growth, it is important that appropriate dose adjustments are possible. This may be done using an oral solution, or with combinations of tablets at different strengths. Several drugs are difficult to use due to the lack of appropriate tablet formulations.

For previously untreated children the first-line recommendations are: 2 NRTIs (abacavir + lamivudine) + 1 NNRTI (nevirapine if <3 y of age, efavirenz if ≥ 3 y) *or* 2 NRTIs (abacavir + lamivudine) + 1 PI/r (lopinavir/r).

- Concerning NRTIs, the combination of abacavir + lamivudine has a better adverse effects profile and is more efficacious than is zidovudine + lamivudine [52].

Table IV. Clinical classification of children and adolescents <13 y.

Category Symptoms	N None	A Mild	B Moderate	C Severe
	≤ 1 av A	• Lymphadenopathy • Hepatomegaly • Splenomegaly • Dermatitis • Parotitis • Recurrent URI	• Serious bacterial infection • Oral candidiasis >2 months of age • Repeated diarrhoea • Hepatitis • Nephropathy • Cardiomyopathy • HZ or HSV ≥ 2 episodes • LIP • Fever • Anaemia <80 g/l • Thrombocytopenia $<100 \times 10^9$/l • Neutropenia $<1 \times 10^9$/l	All AIDS-defining conditions excepting LIP, e.g.: • Repeated serious bacterial infections • Candidiasis in oesophagus or lungs • CMV >1 month of age • Kaposi's sarcoma • Lymphoma • Disseminated or extrapulmonary TB • Cerebral toxoplasmosis • Disseminated MAC • PCP • Progressive multifocal leukoencephalopathy • Wasting syndrome

URI, upper respiratory tract infection; HZ, herpes zoster; HSV, herpes simplex virus; LIP, Lymphoid interstitial pneumonitis; CMV, cytomegalovirus; TB, tuberculosis; MAC, Mycobacterium avium complex; PCP, Pneumocystis pneumonia.
Modified from the Centers for Disease Control and Prevention (CDC) classification, 1994.

- Abacavir and lamivudine are now available as tablets with a score-line, which greatly facilitates dosing in growing children.
- Testing for HLA-B*5701 should be performed prior to abacavir initiation, and this drug should not be used if positive [12]. Zidovudine + lamivudine is recommended in such cases.
- Due to inadequate documentation of safety and pharmacokinetics, tenofovir should, if possible, not be used in children, but can be used in post-pubertal youths.
- Emtricitabine can be used in children and adolescents weighing at least 33 kg.
- Stavudine and zidovudine (excepting HLA-B*5701-positive patients) should not be used for first-line treatment of antiretroviral-naïve children and adolescents.
- The choice between NNRTI and PI/r should be governed by the same concerns as in adults.

Prophylaxis against opportunistic infections

Prophylaxis against Pneumocystis jiroveci should be given as follows:

- <1 y of age: initiated regardless of immune status.
- 1–4 y: initiated if CD4 <15% or $<500 \times 10^6$ cells/l.
- ≥5 y: initiated if CD4 <15% or $<200 \times 10^6$ cells/l.

As an alternative to oral co-trimoxazole, dapsone or inhaled/intravenous pentamidine may be used in special cases. Routine primary prophylaxis against other opportunistic infections is not recommended.

Follow-up

The follow-up of HIV-infected children and adolescents requires a high level of competence in the field of HIV medicine, as well as in paediatrics. Apart from the antiretroviral therapy, the child and its parents also need access to paediatric medical and psychosocial care. In Sweden, national educational activities for children and adolescents (HIV-school) are arranged by the National Competence and Resource Centre for Children and Adolescents with HIV, at the Karolinska University Hospital. In most cases, the children are monitored clinically, virologically and immunologically (plasma HIV-RNA and CD4 cells) approximately every third month. In the case of clinical symptoms, suspected side effects of drugs, adherence problems, or very high levels of viraemia, more frequent monitoring may be necessary, since immune function may deteriorate rapidly. The recommendations for laboratory monitoring are not substantially different from those of adult HIV care. It is important that InfCare HIV also be used for the follow-up of paediatric patients. A slightly modified version is available for paediatric HIV care.

Post-exposure prophylaxis (PEP)

PEP may be indicated when a needle stick incident results in penetration of the skin with an HIV-contaminated instrument, or following unsafe sex with an HIV-infected person (evidence level 3b, recommendation level B), or when an injection needle has been shared with a drug user who is HIV-infected (evidence level 5, recommendation level D). PEP may also be occasioned if mucous membranes or injured skin has been exposed to HIV-infected blood (recommendation level D).

The risk of infection in the case of a needle stick incident or condom rupture is very small if the index patient is undergoing effective antiretroviral therapy and has stably undetectable viraemia. If this can be verified, one may consider withholding PEP.

If antiretroviral treatment is deemed necessary, it should start immediately and be handled as an emergency. When more than 36 h have passed since the incident, PEP is not indicated (evidence level 3b, recommendation level B). Consultation with a physician experienced in the treatment of HIV is recommended.

Treatment with zidovudine + lamivudine + tenofovir, or with another drug combination adapted to the particular resistance pattern of the index patient and/or the present and previous treatment of the index patient, should be given for 4 weeks (recommendation level D). Choosing between Combivir® + Viread® or Truvada® + Retrovir®, the latter is preferable, as zidovudine can then be given at the lower dose of 250 mg, which reduces the risk of side effects.

A rapid initiation of treatment is essential. If any of the above-mentioned drugs are not available, or if there is uncertainty about the activity of this drug combination against the index strain, another triple drug combination should be given. However, due to the risk of serious adverse events, abacavir and nevirapine should not be used for PEP.

If PEP is administered, the person at risk should be tested for HIV antibodies on the first day of exposure (day 0) and followed-up at 6, 12, and 24 weeks thereafter. If PEP is not given, the Swedish Institute for Infectious Disease Control (SMI, Smittskyddsinstitutet) recommends a follow-up period of 3 months. The reason for monitoring a PEP-treated person until 24 weeks is that the development of antibodies may be slowed when treatment has been given. The above recommendation for the duration of follow-up

post-PEP is based on a conservative estimate of the risk of late seroconversion. It is of vital importance that psychological support is provided during the full duration of the follow-up, but particularly during the first 4 weeks, which, according to experience, are associated with the greatest psychological stress.

Treatment of primary HIV infection (PHI)

No study has demonstrated any benefit of early treatment of PHI. Patients with pronounced symptoms when presenting with PHI have a worse prognosis than patients without symptoms (evidence level 2b). In the event of an early diagnosis of symptomatic PHI, immediate treatment may be considered, but the value of this intervention is uncertain.

Concomitant treatment of HIV and mycobacterial infections

There are significant interactions between antiretroviral and anti-mycobacterial drugs. When tuberculosis (TB) has been diagnosed in an untreated HIV-positive patient, anti-mycobacterial treatment should be initiated first, and if antiretroviral therapy is indicated, it should then be commenced as soon as possible (evidence level 2a). When HIV and TB are treated simultaneously, the drugs for mycobacterial infections should be chosen, and their dosage adjusted, in consideration of their interactions with antiretroviral drugs.

Recommended regimens for concomitant treatment of HIV and TB include:

- Efavirenz dosed at 800 mg once daily (+2 NRTIs), together with anti-mycobacterials at normal doses.
- Isoniazid 300 mg once daily.
- Rifampicin 450–600 mg once daily.
- Ethambutol 15 mg/kg once daily (discontinued if no TB drug resistance is found).
- Pyrazinamide 1500–2000 mg once daily (discontinued after 2 months of treatment).

or

- A PI/r (+ 2 NRTIs) together with anti-mycobacterials, where rifabutin is substituted for rifampicin (the other anti-mycobacterials as above). The PI/r is given at normal dose. Rifabutin should be given at 150 mg three times weekly (see the SPCs for the relevant drugs, as dosing recommendations may change on the basis of emerging data).

The use of efavirenz is favoured above PI/r due to better documentation and lower cost.

When treating atypical mycobacteria, rifabutin is always preferred to rifampicin. The recommendation is as follows:

- Efavirenz at normal dose (600 mg once daily) (+2 NRTIs) together with
- Rifabutin 300 mg once daily.
- Clarithromycin 500 mg twice daily.
- Ethambutol 15 mg/kg once daily.

or

- A PI/r at normal dose (+ 2 NRTIs)
- Rifabutin 150 mg, three times weekly, with clarithromycin and ethambutol as above.

Azithromycin is an alternative to clarithromycin; however the cost is higher and the optimal dose has not been determined. When treating atypical mycobacteria, the choice of NNRTI- or PI/r-based therapy does not greatly impact cost.

HIV treatment in the presence of hepatitis B virus or hepatitis C virus co-infection

Hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infections are common, since their routes of transmission are the same as those for HIV. In Sweden, approximately 5% of HIV patients are co-infected with HBV and about 20% with HCV, the prevalence of co-infection being higher in certain groups such as intravenous drug users and haemophiliacs (InfCare HIV, September 2008). The survival rate of HIV patients has improved significantly since the advent of antiretroviral therapy. However, patients with HIV infection have a faster rate of progression of liver injury due to chronic viral hepatitis than do patients who are HIV-negative [53]. As a consequence, liver-related complications associated with HBV and HCV have become a primary cause of morbidity and mortality in co-infected patients [54].

Tenofovir, lamivudine and emtricitabine have clinically relevant activity against both HBV and HIV. The nucleoside analogues with the indication HBV (but not HIV) also have varying levels of activity against HIV, which leads to a risk of development of HIV drug resistance (adefovir – possible risk of tenofovir resistance; entecavir – risk of resistance to lamivudine/emtricitabine). Telbivudine may be an exception to this, but it is not considered a first-line alternative for HBV treatment.

From these considerations it follows that:

- *With hepatitis C co-infection*, the possibility of HCV therapy should always be considered. Absolute contraindications are uncommon, and not principally different in co-infected patients.
- An earlier initiation of antiretroviral therapy should be considered, particularly if there is not enough time to treat the HCV co-infection while the CD4 cell count is still high, or if HCV treatment is not feasible or has failed.
- *With hepatitis B co-infection*, all patients who are in need of treatment for either infection should receive drug regimens that are maximally effective against both HBV and HIV. In practice, this means that tenofovir+emtricitabine should be a component of the antiretroviral therapy unless there are contraindications.
- Peg-interferon monotherapy may be considered for selected patients who are in need of HBV therapy, but have high CD4 cell counts.

Vaccination against hepatitis B and hepatitis A

HIV-infected patients with no previous or ongoing HBV infection should be immunized against HBV (recommendation level B). In patients with advanced HIV, the immunization response may be insufficient, and additional doses may be needed in order to achieve a protective anti-hepatitis B surface antigen (anti-HBs) level [55]. An alternative strategy in such patients is to delay vaccination until the CD4 cell count has increased due to antiretroviral therapy. The vaccine response almost equals that seen in HIV-negative individuals when the CD4 cell count is >500 cells/μl. Co-infected patients with HIV, HBV and/or HCV should be immunized against hepatitis A.

Treatment of HIV-2 infection

The development of immune deficiency is much slower in HIV-2 infection than with HIV-1. Many HIV-2 infected patients will probably never need antiretroviral therapy. However, when treatment is indicated, there are several specific problems that need to be considered. Due to the absence of informative clinical trials, the knowledge on optimal treatment of HIV-2 is limited. The recommendations that follow are mainly based on in vitro data, and on clinical experience reported from France, Spain and Portugal.

- The restitution of CD4 cells appears to be lower when treating HIV-2, as compared to HIV-1. For this reason, it may be prudent to consider treatment at higher CD4 cell counts. However, there is no scientific basis for any specific recommendation.
- NNRTIs: all available drugs, including etravirine, are devoid of activity against HIV-2.
- NRTIs: all available drugs appear to have clinically relevant anti-HIV-2 activity. However, the genetic barrier to resistance appears to be lower for HIV-2, where the K65R and Q151M mutations occur more frequently.
- PI/r: lopinavir, darunavir and saquinavir appear to have clinically relevant activity against HIV-2, whereas that of the other PIs appears limited. The genetic barrier to resistance seems lower than in HIV-1, at least for lopinavir.
- Entry and integrase inhibitors: enfuvirtide lacks activity against HIV-2, whereas raltegravir appears to have clinically relevant activity, though in vivo data are very limited. No information is available concerning maraviroc.
- Clinical experience implies that treatment failure is more common in HIV-2 than in HIV-1.
- Resistance testing is not available for HIV-2. While sequencing is technically possible, the knowledge on how to interpret the data is very limited.
- Arguably, adherence is even more important when treating HIV-2, since the genetic barrier to resistance is lower, as is the availability of effective second-line therapy.
- A reasonable regimen for a treatment-naïve patient with HIV-2 would be 2 NRTIs (abacavir/lamivudine or tenofovir/emtricitabine, together with lopinavir/r or darunavir/r). One may also consider adding raltegravir to the regimen.

Drug interactions

The great potential of PIs and NNRTIs for drug interactions necessitates a thorough assessment of all the drugs taken by the patient when antiretroviral treatment is initiated or modified; this also pertains to situations when concentration-dependent side effects of a drug are suspected. There are several websites that provide information on HIV drug interactions, including the free-of-charge http://www.druginteractions.org, and http://www.clinicalpharmacology.com, for which a fee is charged.

NRTIs

The NRTIs primarily interact with each other. Co-treatment with the NRTI-pairs zidovudine+stavudine (thymidine analogues), lamivudine+emtricitabine (cytidine analogues) and tenofovir+

didanosine (adenosine analogues), are contraindicated, due to the absence of additive/synergistic effects or a risk of deleterious drug interactions [28] (Viread® SPC). Ribavirin should not be combined with abacavir (risk of reduced ribavirin efficacy), didanosine (increased risk of lactic acidosis) or zidovudine (increased risk of anaemia) [37,56].

NNRTIs

Available NNRTIs induce several cytochrome P450 (CYP450) enzymes, which may result in decreased concentrations of co-administered medications that are eliminated via metabolism. A clinically important example is methadone (the levels of which can also be decreased by PI/r therapy, though usually to a smaller extent). Co-treatment with NNRTIs and PI/r may require dose alterations due to enzyme induction (the SPCs of the respective agents should be consulted for dosing recommendations).

PIs

It is recommended that PIs always be combined with ritonavir in the booster dose (100–200 mg four times daily or twice daily). Ritonavir is a very potent inhibitor of cytochrome P3A (CYP3A); thus it greatly increases the PI exposure ('boosting'), which improves treatment results and reduces the risk of resistance in the event of virological treatment failure. However, ritonavir boosting gives rise to a plethora of potential drug interactions. Some drugs are contraindicated when treating with PI/r, whereas others require dose adjustments. When co-prescribing to patients treated with PI/r, the risk of drug interactions should always be kept in mind. As mentioned above, several web-based interaction databases are available, as is the possibility of consulting a clinical pharmacologist. Examples of clinically important interactions include:

- Statins: simvastatin and lovastatin are contraindicated with concomitant PI/r therapy. The first-line statin choice in most cases is pravastatin. However, when co-treating with darunavir/r, the first-line statin choice is atorvastatin at 10 mg once daily. Exposure to rosuvastatin is also increased; when co-treating the initial rosuvastatin dose should be low, and the patient should be carefully monitored for adverse effects.
- Antihypertensives: increased exposure to calcium channel blockers, which should be used with caution. For beta-blockers, diuretics and angiotensin-converting enzyme (ACE)-inhibitors, clinically relevant interactions are not expected.
- Benzodiazepines: increased exposure to, e.g., diazepam, alprazolam, flunitrazepam, and several other agents. Oxazepam is an exception, and is recommended at a dose titrated by clinical response.
- Inhalational steroids (including nasal administration): the concomitant use of highly potent corticosteroids such as fluticasone and PI/r has been associated with Cushing syndrome. Beclomethasone is an alternative that is not expected to interact with PI/r (Norvir® SPC).

Absorption of atazanavir is acid-dependent. Co-administration of ritonavir-boosted atazanavir and omeprazole reduced atazanavir exposure by approximately 75%. Therefore co-treatment with proton pump inhibitors is contraindicated in patients on atazanavir. When co-treating with H2-blockers or buffering antacids, the dosing should be timed in such a way that the ventricle is not alkaline (pH >3–4) at the time of passage of atazanavir. For instance, atazanavir should be administered >2 h prior to, and >10 h after, the intake of an H2-blocker; with buffering antacids, atazanavir should be given >2 h prior or >1 h after administration.

Interactions with oral contraceptives

Ritonavir induces the metabolism of norethisterone and of ethinyl oestradiol [57]. Efavirenz significantly lowers the exposure to progestins (Sustiva® SPC). The clinical relevance of these interactions is unknown, but a reduced effect of the oral contraceptives cannot be excluded. Other forms of contraception should be used when treating with PI/r or NNRTIs.

Food interactions

Several antiretroviral drugs interact significantly with dietary elements. Tenofovir, as well as all the PIs (excluding the lopinavir/r tablet), should be taken with a meal, since the bioavailability in the fasting state is lower. The didanosine enterocapsules, however, are recommended to be taken fasting, since drug exposure is otherwise reduced by 19–27%. Available data, however, indicate that this may not be clinically relevant [58]. In order to decrease the risk of CNS side effects during efavirenz treatment, it is generally recommended that efavirenz be taken fasting. This does not greatly affect the total drug exposure, but lowers the peak concentration, which may attenuate the adverse effects.

Interactions with herbal remedies

Several studies have demonstrated that St. John's wort (*Hypericum perforatum)* is a potent inducer of CYP450 enzymes and transport proteins (e.g., P-glycoprotein). Therefore, this particular herbal medicine is contraindicated in patients taking PIs or NNRTIs. In general, knowledge of the risks associated with interactions between drugs and herbal medicines is very limited. Because of this, general caution is recommended regarding their use during antiretroviral therapy.

Therapeutic drug monitoring

Routine measurement of plasma concentrations of antiretroviral drugs is not recommended, as the value of this is questionable. However measuring drug levels may be considered in the following situations:

- Concomitant treatment with potent inducers of drug metabolism (e.g., rifampicin, carbamazepine, phenytoin) or other substances known to significantly lower exposure to the antiretroviral drugs.
- Treatment of pregnant women or paediatric patients when there is clinically relevant drug resistance.
- When there are adverse effects that may be concentration-dependent (e.g., efavirenz-associated CNS effects or atazanavir-induced icterus).
- In patients with significant hepatic or renal dysfunction.
- In patients failing PI therapy.

Samples should generally be taken in steady state, and as a practical guideline, at least 7–14 days of therapy may be recommended. Trough sampling is primarily recommended, as this may correlate best with effects, and show the least variability.

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