Once-daily antiretroviral therapy: Spanish Consensus Statement


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Background: Administration of antiretroviral therapy (ART) once daily is creating extraordinary interest among the members of the scientific community and also among those who receive the therapy. However, in clinical practice, some doubts remains about its use.

Objectives: This document examines the characteristics and possibilities of treatment administered once daily.

Methods: Consensus of 248 Spanish experts in the field.

Results: Once-daily dosing is considered an added value which could favour adherence and, therefore, efficacy, as well as the quality of life of certain patients, however, the objective of adequate adherence in the long term is often difficult to achieve regardless of the treatment used. In theory, any patient can receive once-daily therapy, although some patients could particularly benefit from it, e.g. those with unfavourable social or personal circumstances, including drug users, patients whose treatment must be supervised, patients receiving multiple medications, or those who need rescue therapy after multiple treatment failures. At present, it is possible to design once-daily ART using some of the combinations of drugs considered as first-choice in national and international recommendations for antiretroviral therapy, but the options are still limited. The marketing of new drugs with this characteristic could allow us to increase the number and types of patient who can benefit from once-daily regimens, including those patients who need rescue therapy.

Conclusions: Once-daily ART is a good alternative to regimens administered several times each day when a potent combination of active drugs is available.

Keywords: HIV therapy, antiretrovirals, HAART

Introduction

Since the introduction of highly active antiretroviral therapy (HAART) as the standard for HIV treatment,1,2 one of the main concerns of both physicians and patients has been the availability of well-tolerated medications with a convenient dosing schedule which can be adapted to the patient’s lifestyle.3 The pharmaceutical industry has made a considerable research effort, which has led to both the development of new medications and improvement of the formulation of older drugs. As a result, HIV therapy has become

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simpler in recent years. Pill burden, dietary restrictions and, in some cases, number of daily doses have all been reduced, although most patients still receive more than one dose per day.

Current therapy is potent and its efficacy is high when adherence is optimal, as has been demonstrated with directly observed treatments. Experience with the treatment of chronic conditions in different areas of medicine has taught us that the fewer the daily doses necessary, the better the adherence. Given the ability of HIV to rapidly escape from drug pressure, the level of adherence required to maintain virological suppression is high in HIV infection, in order of 95% and higher. The availability of drugs that can be administered once daily has been increasing in recent times. It seems reasonable to anticipate that a well-tolerated regimen using drugs that can be simultaneously administered once daily will optimize adherence to treatment by fitting the lifestyle of most patients and improving their quality of life.

Administration of antiretroviral therapy (ART) once daily is creating extraordinary interest among members of the scientific community and also among those who receive the therapy. However, in clinical practice, some physicians are still somewhat apprehensive about administering therapy once daily, whereas others use medicines which have not yet been approved by the regulatory bodies for once-daily use. This document examines the characteristics and possibilities of treatment administered once per day, with the consensus of 248 Spanish experts in the field.

Methodology

The paucity of objective information on the role of once-daily dosing in HIV patient care and ART led to the need for a methodology essentially focused on expert opinion. In order to reduce as much as possible the bias in opinion, a large number of physicians attending HIV patients in Spain were included in the discussion.

Two of the authors (FP and ER), who promoted the document, selected 18 physicians with well known expertise in antiretroviral therapy representing most of the geographical areas in Spain, including those attending HIV patients in prison, to create a coordinator committee. The committee designed a questionnaire and invited Spanish HIV physicians working both full-time and part-time to participate in a series of consensus meetings.

A total of 23 meetings were held (21 regional meetings and two meetings of prison physicians), with 248 participating physicians (8 to 15 per meeting). A common discussion outline was adopted for the meetings. The moderator manually recorded the opinion of the participants in the minutes and these were circulated following the meeting for approval.

The moderators later met to pool the opinions expressed by each of the regional groups, and tried to find those areas of agreement which reflected the consensus of the participants, as well as the doubts and disagreements which arose. The moderators’ meeting was in turn coordinated by two of the participating physicians, whose job was to record the consensus for the present document. The final document was written by the two global coordinators (FP and ER) and approved by all the coordinating committee members.

Statements without a reference citation reflect the consensus opinion of the moderators’ panel.

The levels of evidence and grading of recommendations used are shown in Table 1.

Efficacy

Is once-daily therapy an added value in itself?

Therapeutic efficacy is a basic parameter in any medical intervention. HIV infection has some particular connotations and the convenience of a once-daily regimen is, in itself, an added value which can have a positive effect on adherence to treatment (Level of evidence IV).

Does once-daily dosing improve efficacy?

ART is influenced by several inter-related factors which depend on the characteristics of the treatment (potency, toxicity, pill burden, number of doses, dietary requirements), the patient (adherence, pharmacokinetics, genetic factors) and the virus (resistance, virulence). Many of these factors improved in some twice-daily regimens and several recent randomized trials showed a very high efficacy with these regimens [viral load < 50 copies/mL at 48 weeks of follow-up in 65–85% of patients by intention-to-treat (ITT) analysis]. However, some of these regimens were administered twice daily due to demands of the study (double-blind, placebos), but the drugs used could have been administered once daily. The high degree of success shown by these trials leaves little room to demonstrate a significant improvement with once-daily dosing. One could speculate for example that changing from once-daily to twice-daily dosing improves virological outcomes by 3–5%. For a clinical trial to show that these differences are significant, about 950–2700 patients would be necessary per treatment group. Therefore, it is practically impossible to demonstrate the superiority of a once-daily dosing schedule over a twice-daily schedule using the same drugs. If we compare regimens with different drugs, different potency, different pill burden, different toxicity, etc., it might be easy to obtain a significantly higher efficacy, although, in this case, we would no longer be comparing only a once-daily schedule with a twice-daily schedule, but we would also have to take into account the sum of many different factors.

Although finding significant improvements in efficacy when using once-daily therapy is not easy, authors agree that efficacy
of once a day therapy must be at least non-inferior to twice-daily regimens, and their greater convenience seems reason enough to choose this approach if available (Level of evidence IV).

**Durability of the response**

Several trials with twice-daily or once-daily regimens demonstrated the maintenance of good efficacy for as long as 3 or even 5 years of follow-up. The durability of efficacy depends mainly on adherence, potency and toxicity in the long term. Long-term adherence of a more convenient treatment regimen is expected to be better than that of a less convenient regimen. Potency is not inferior and long-term toxicity is no greater in once-daily regimens than in twice-daily regimens. Therefore, it is reasonable to think that the durability of a once-daily regimen will be the same or greater than that of a twice-daily regimen (Level of evidence IV).

**Drugs approved for once-daily administration**

Table 2 shows the list of ART drugs which have been approved by regulatory authorities in Europe (European Medicines Agency (EMEA)) and the United States (Food and Drug Administration (FDA)), those which have not yet been approved but whose once-daily use is supported by clinical and pharmacokinetic studies and those which will probably never be used in once-daily regimens, together with the recommended once-daily and twice-daily doses and the daily pill burden. Atazanavir (ATZ), boosted or not boosted with ritonavir (RTV), is the only protease inhibitor (PI) exclusively approved for once-daily administration. Fosamprenavir boosted with ritonavir has been approved by the FDA for once-daily dosing only in naive patients, however fosamprenavir once daily has not been approved in Europe. The once-daily administration of some approved (amprenavir, lopinavir) or not approved (indinavir, saquinavir, atazanavir + saquinavir) protease inhibitors could be useful for patients when once-daily dosing is particularly important, although many patients may prefer to take the medication in two doses because of a heavy pill burden (Level of evidence III).

**Possible regimens**

To recommend a therapeutic regimen, it must be backed up by clinical studies. Table 3 shows the studies carried out with protease inhibitor-sparing regimens administered, or which can be administered, once daily, and their clinical efficacy.

The combination of didanosine (ddI) + lamivudine (3TC) + efavirenz (EFV) has been used in four studies with a total of 214 naive HIV-infected patients. At week 48 of treatment, 77–80% of the patients had a plasma viral load of <50 copies/mL (ITT; non-completer = failure (nc = f)). One of the three is a randomized study which compares this regimen with another two: one twice daily with a low pill burden [zidovudine (ZDV)/3TC/EFV], and the other, twice daily with a high pill burden [ZDV/3TC/nelfinavir (NFV)]. The efficacy of ddI/3TC/EFV is similar to that of the low-burden, twice-daily regimen and greater than that of the high-burden, twice-daily regimen.

In a non-comparative study, the efficacy of ddI/3TC/nevirapine (NVP) once daily was analysed in 70 naive patients and, at

### Table 2. Potential once-daily antiretroviral drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose twice daily (mg)</th>
<th>Dose once daily (mg)</th>
<th>Daily pill burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Approved by the FDA and/or the EMEA for once-daily administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abacavir (ABC)</td>
<td>300</td>
<td>600</td>
<td>2</td>
</tr>
<tr>
<td>didanosine (ddI)</td>
<td>–</td>
<td>250–400</td>
<td>1</td>
</tr>
<tr>
<td>emtricitabine (FTC)</td>
<td>–</td>
<td>200</td>
<td>1</td>
</tr>
<tr>
<td>lamivudine (3TC)</td>
<td>150</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>stavudine (d4T) XR</td>
<td>–</td>
<td>100–75</td>
<td>1</td>
</tr>
<tr>
<td>tenofovir (TDF)</td>
<td>–</td>
<td>300</td>
<td>1</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>–</td>
<td>600/300</td>
<td>1</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>–</td>
<td>300/200</td>
<td>1</td>
</tr>
<tr>
<td>efavirenz (EFV)</td>
<td>–</td>
<td>600</td>
<td>1</td>
</tr>
<tr>
<td>atazanavir (ATZ) ± ritonavir (RTV)</td>
<td>–</td>
<td>400–300 + 100</td>
<td>2–3</td>
</tr>
<tr>
<td>amprenavir (APV) + RTV</td>
<td>600 + 100</td>
<td>1200 + 200</td>
<td>10</td>
</tr>
<tr>
<td>fosamprenavir + RTV</td>
<td>700 + 100</td>
<td>1400 + 200</td>
<td>4</td>
</tr>
<tr>
<td>lopinavir (LPV) + RTV</td>
<td>400 + 100</td>
<td>800 + 200</td>
<td>6</td>
</tr>
<tr>
<td>(b) Not approved, but with studies which support once-daily administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nevirapine (NVP)</td>
<td>200</td>
<td>400</td>
<td>2</td>
</tr>
<tr>
<td>indinavir (IDV) + RTV</td>
<td>800 + 100</td>
<td>variable</td>
<td>5–7</td>
</tr>
<tr>
<td>saquinavir (SQV) + RTV</td>
<td>1000 + 100</td>
<td>variable</td>
<td>7–12</td>
</tr>
<tr>
<td>ATZ + SQV + RTV</td>
<td>–</td>
<td>variable</td>
<td>8–11</td>
</tr>
<tr>
<td>(c) Not approved, not able to be administered once daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stavudine (d4T)</td>
<td>30–40</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>zidovudine (ZDV)</td>
<td>250–300</td>
<td>–</td>
<td>2</td>
</tr>
<tr>
<td>non-boosted PIs*</td>
<td>variable</td>
<td>variable</td>
<td>variable</td>
</tr>
</tbody>
</table>

*aExcept atazanavir.*
Molina75 ddI/FTC/EFV 178 non-comparative simplification no 519 87% 13
Maggiolo69 ddI/3TC/EFVa 75 non-comparative naive no 251 77% 208
in the 14 patients with under 100 CD4 lymphocytes/mm³ at
Jayaweera41 d4TXR/3TC/EFV 70 non-comparative naive >100 351 71% 174
Barlett76 ABC/3TC/EFVb,c 97 randomized naive >50 307 76% NA
Ribera73 ddI/3TC/NVP 70 non-comparative naive no 286 69% 176
Maggiolo71 ddI/3TC/EFV 34 randomized naive no 184 77% 194
Landman70 ddI/3TC/EFV 40 non-comparative naive >50 164 77% 200
Saag22 ddI/FTC/EFV 286 randomized naive no 312 78% 194
Molina75 ddI/3TC/EFV 40 non-comparative naive no 276 76% 203
Molina75 ddI/FTC/EFV 178 non-comparative simplification no 519 87% 13
Gallant21 TDF/3TC/EFVb,c 299 randomized naive no 307 76% NA
Ribera73 ddI/3TC/NVP 70 non-comparative naive no 286 69% 176
Negredo82 ddI/TDF/NVP 85 non-comparative simplification no 660 76% –95
Moyle24 ABC/3TC/EFVb 384 randomized naive no 262 66% 188
DeJesus25 ABC/3TC/EFVb,c 324 randomized naive no 264 70% 209
Barlett76 ABC/3TC/EFVb,c 97 randomized naive no 307 76% NA
Podzamczer77 ABC/3TC/EFVb,c 115 randomized naive no 203 64% 203
Jayaweera21 d4TXR/3TC/EFV 70 non-comparative naive no 351 71% 174

Table 3. Clinical experience with protease inhibitor-sparing regimens which can be administered once daily

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n</th>
<th>Type of study</th>
<th>Clinical scenario</th>
<th>CD4 inclusion criterion</th>
<th>Baseline CD4 (cells/mm³)</th>
<th>Efficacy at 48 weeks (VL &lt; 50 copies/mL, ITT nc = f)</th>
<th>Increase in CD4 at 48 weeks (cells/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maggiolo69</td>
<td>ddI/3TC/EFV</td>
<td>75</td>
<td>non-comparative</td>
<td>naive</td>
<td>no</td>
<td>251</td>
<td>77%</td>
<td>208</td>
</tr>
<tr>
<td>Landman70</td>
<td>ddI/3TC/EFV</td>
<td>40</td>
<td>non-comparative</td>
<td>naive</td>
<td>&gt;50</td>
<td>164</td>
<td>77%</td>
<td>184</td>
</tr>
<tr>
<td>Maggiolo71</td>
<td>ddI/3TC/EFV</td>
<td>34</td>
<td>randomized</td>
<td>naive</td>
<td>no</td>
<td>184</td>
<td>77%</td>
<td>194</td>
</tr>
<tr>
<td>Ward72</td>
<td>ddI/3TC/EFV</td>
<td>65</td>
<td>non-comparative</td>
<td>naive</td>
<td>&gt;100</td>
<td>311</td>
<td>80%</td>
<td>217</td>
</tr>
<tr>
<td>Saag22</td>
<td>ddI/FTC/EFV</td>
<td>286</td>
<td>randomized</td>
<td>naive</td>
<td>no</td>
<td>312</td>
<td>78%</td>
<td>168</td>
</tr>
<tr>
<td>Molina74</td>
<td>ddI/FTC/EFV</td>
<td>40</td>
<td>non-comparative</td>
<td>naive</td>
<td>&gt;100</td>
<td>373</td>
<td>93%</td>
<td>200</td>
</tr>
<tr>
<td>Molina75</td>
<td>ddI/FTC/EFV</td>
<td>178</td>
<td>non-comparative</td>
<td>simplification</td>
<td>no</td>
<td>519</td>
<td>87%</td>
<td>13</td>
</tr>
<tr>
<td>Gallant21</td>
<td>TDF/3TC/EFVb,c</td>
<td>299</td>
<td>randomized</td>
<td>naive</td>
<td>no</td>
<td>276</td>
<td>76%</td>
<td>NA</td>
</tr>
<tr>
<td>Ribera73</td>
<td>ddI/3TC/NVP</td>
<td>70</td>
<td>non-comparative</td>
<td>naive</td>
<td>no</td>
<td>286</td>
<td>69%</td>
<td>176</td>
</tr>
<tr>
<td>Negredo82</td>
<td>ddI/TDF/NVP</td>
<td>85</td>
<td>non-comparative</td>
<td>simplification</td>
<td>&gt;100</td>
<td>660</td>
<td>76%</td>
<td>–95</td>
</tr>
<tr>
<td>Moyle24</td>
<td>ABC/3TC/EFVb</td>
<td>384</td>
<td>randomized</td>
<td>naive</td>
<td>&gt;50</td>
<td>262</td>
<td>66%</td>
<td>188</td>
</tr>
<tr>
<td>DeJesus25</td>
<td>ABC/3TC/EFVb,c</td>
<td>324</td>
<td>randomized</td>
<td>naive</td>
<td>&gt;50</td>
<td>264</td>
<td>70%</td>
<td>209</td>
</tr>
<tr>
<td>Barlett76</td>
<td>ABC/3TC/EFVb,c</td>
<td>97</td>
<td>randomized</td>
<td>naive</td>
<td>&gt;50</td>
<td>307</td>
<td>76%</td>
<td>NA</td>
</tr>
<tr>
<td>Podzamczer77</td>
<td>ABC/3TC/EFVb,c</td>
<td>115</td>
<td>randomized</td>
<td>naive</td>
<td>no</td>
<td>203</td>
<td>64%</td>
<td>203</td>
</tr>
<tr>
<td>Jayaweera21</td>
<td>d4TXR/3TC/EFV</td>
<td>70</td>
<td>non-comparative</td>
<td>naive</td>
<td>&gt;100</td>
<td>351</td>
<td>71%</td>
<td>174</td>
</tr>
</tbody>
</table>

VL, HIV-1 RNA plasma viral load; NA, not available.
*a*d4T (300 mg/day) was administered in buffered tablets (regardless of weight).
*b*Placebo was administered twice daily.
*c*3TC was administered twice daily.
*d*Week 24.

48 weeks, 69% of patients had a viral load in plasma of <50 copies/mL (ITT; nc = f). Efficacy was 77% in the 56 patients with a baseline CD4 lymphocyte count of >100 cells/mm³ and 29% in the 14 patients with under 100 CD4 lymphocytes/mm³ at baseline.73

The combination ddI/emtricitabine (FTC)/EFV has been used in two studies which include a total of 326 naive patients22,74 and in a treatment simplification study.75 At 48 weeks of treatment, 79% of naive patients presented a plasma viral load of <50 copies/mL (ITT; nc = f). One of the two studies is randomized and the efficacy of ddI/FTC/EFV is greater than that of ddI/stavudine (d4T)/EFV.22 In the simplification study, the efficacy of simplification was superior to that of continuing the previous treatment with a protease inhibitor.75

Tenofovir (TDF)/3TC/EFV has been used in a randomized, double-blind study with 600 patients, although lamivudine was administered twice daily and stavudine was included as a placebo.21 The efficacy of this regimen was the same as that of d4T/3TC/EFV, with lower mitochondrial toxicity.

A recent study has shown a higher proportion of naive patients with viral load of <50 copies/mL (48 weeks, ITT; nc = f) if they were randomized to TDF/FTC/EFV (77%) when compared with those assigned to ZDV/3TC/EFV (68%).23

There have been four randomized studies in naive patients receiving abacavir (ABC)/3TC/EFV, although in none of them is all the treatment administered once daily, either because of a twice-daily placebo or because one of the drugs is administered twice daily. The first, a double-blind study, compares abacavir once daily with abacavir twice daily, and reveals the same efficacy.24 The second compares abacavir with ZDV/3TC/EFV and also observes the same efficacy and a greater increase in the number of CD4 lymphocytes with abacavir than with zidovudine.25 In the third, ABC/3TC proved to be more efficacious with efavirenz than with amprenavir (APV)/RTV or with stavudine.76 In the fourth study, abacavir was compared with stavudine, both combined with lamivudine and efavirenz, and a similar efficacy was observed.77

A combination of nucleosides, which because of its posology, resistance profile and its a priori intrinsic potency appeared promising for once-daily ART regimens is TDF/ddI. However, an unexpected pharmacokinetic interaction was observed between these drugs, with an increase in intracellular and plasma concentrations of didanosine, no modification of the concentrations of tenofovir and an increase in toxicity.78–81 To reach plasma concentrations similar to those reached with standard doses of both drugs administered individually, it is necessary to reduce the dose of didanosine to 250 mg in patients who weigh more than 60 kg and to 200 mg in patients <60 kg. Tenofovir and didanosine have been used mainly in treatment simplification regimens.82–84 In patients who received standard doses (non-corrected) of both drugs, a reduction in the number of CD4 lymphocytes was observed from the sixth month of treatment onward despite an undetectable viral load.82–84 Three recent studies have shown a high early virological failure and the occurrence of resistance mutations in naive patients treated with tenofovir, didanosine and efavirenz or nevirapine, particularly in those with advanced disease (high viral load, low CD4 cell count and AIDS diagnosis previous to treatment).85–87 In view of these results, the EMEA and the pharmaceutical companies issued a caution regarding the co-administration of TDF and ddI in any antiretroviral combination. If this combination is considered strictly necessary, patients should be monitored very closely to ensure that the regimen is effective and they are not developing side effects (Grading of recommendation A).
Some studies have also been carried out with regimens which can be administered once daily, including boosted protease inhibitors [lopinavir (LPV), ampranavir (APV)] and with some unconventional combinations (SQV/RTV/EFV, NVP/EFV/ddI, adebovir/3TC/ddI/EFV). Some of these once-daily regimens may be very useful in special situations. The heavy pill burden is a problem in most of them, and many patients could prefer to take their medication in two doses. The pill burden is lower in regimens where the protease inhibitor is atazanavir or fosamprenavir than in regimens with saquinavir, ampranavir or lopinavir.

The combination of three nucleosides such as TDF/ddI/3TC or TDF/ABC/3TC in once-daily regimens has provided very unfavourable results—around 50% of patients experience virological failure quite quickly, with the appearance of resistance mutations. Therefore, once-daily dosing with three nucleosides should be contraindicated for the moment (Grading of recommendation A).

**Clinical scenarios**

**Do any patient groups in particular benefit from once-daily regimens?**

In theory, any patient can benefit from a once-daily regimen, since it is a simpler therapeutic intervention (Level of evidence IV). However, the benefit could be greater in some patient subgroups (Level of evidence IV), especially: (i) patients who find it difficult or who forget to take some of the prescribed doses (either in the morning or at night); (ii) patients whose lifestyle makes it difficult to set routines; (iii) patients who for social or psychological reasons need the support of third parties to reinforce or guarantee adherence to treatment.

**Possible clinical scenarios in which once-daily dosing could be used**

In naive patients. Most of the data on the use of once-daily drugs and regimens are derived from studies of naive patients (Level of evidence Ib). Using once-daily antiretroviral therapy simplifies explanation to patients. In the case of asymptomatic naive patients, it makes the integration of treatment easier, with no important modification of daily activity. In the increasingly common case of naive patients diagnosed with advanced HIV infection or AIDS, once-daily therapy facilitates the adjustment of concomitant medication (Level of evidence IV).

Nevertheless, even in naive patients, once-daily dosing is not the only argument to be evaluated when choosing a treatment regimen. Other factors, such as efficacy, possible toxicity, pharmacological reactions or concomitant conditions may make it necessary to choose drugs which must be administered twice daily (Level of evidence IV).

In simplification of more complex regimens. There is sufficient evidence indicating that it is both possible and safe to simplify an antiretroviral regimen which includes a protease inhibitor administered twice or three times daily, in favour of simpler protease inhibitor-sparing regimens (Level of evidence Ib). Some of these simpler regimens can be administered once daily.

Some factors support offering once-daily regimens as simplification treatment of specific patients who have adequately controlled viral replication with treatment administered two or more times per day: patients who complain of difficulty in fulfilling the dosing schedule, patients who admit to forgetting to take one of the doses, patients in whom an efficacious treatment must be modified due to intolerance which could be avoided with drugs which can be administered once daily (Level of evidence IV).

Nevertheless, the simplification scenario also has its limitations. It is a strategy whose safety is usually restricted to those patients receiving an efficacious first line of therapy. Currently, there is no evidence to support the view that simplification from a ‘twice-daily non-PI-based’ regimen could have any advantages.

As part of a rescue strategy for patients in therapeutic failure. The priority in patients experiencing therapeutic failure is to design an antiretroviral regimen which is efficacious against viruses with resistance mutations. In this context and with currently available drugs, it is very difficult to obtain a salvage regimen in which all the drugs can be administered in one single dose.

Nevertheless, it is somewhat paradoxical that, in patients who have previously experienced therapeutic failure as a result of poor adherence, more complex treatments are prescribed, thus making it even more difficult to reach an acceptable level of adherence. The availability of simple, highly efficacious regimens in experienced patients must be considered a priority in the development of new drugs and therapeutic strategies (Level of evidence IV).

**Directly observed therapy (DOT).** Observed administration of treatment has been put forward as an efficacious method to guarantee adherence to treatment in specific subgroups of patients.

The availability of ART regimens administered once daily makes this treatment strategy possible, even in the case of patients who are not in an institution (hospitals, prisons or shelters). However, given that ART must be administered for life, the objective of DOT in this setting must be to support patients for a limited period, during critical phases of high risk of inadequate adherence, while they acquire sufficient personal resources to face the challenge of controlling their medication (Level of evidence IV).

**Convenience and adherence with once-daily regimens**

**Does once-daily administration improve adherence?**

Experience in other therapeutic fields shows an inverse relationship between the number of doses prescribed daily and adherence. Data directly related to ART are scarce, as the possibility of preparing complete once-daily regimens is still relatively recent. In an analysis of clinical trials of therapy in naive patients, there was an inverse relationship between the daily pill burden and the efficacy of the regimen. Furthermore, in a survey carried out in Spain, both physicians and patients indicated that a reduction in the number of doses and the pill burden as the most important intervention in improving adherence to antiretroviral therapy.

In a large Spanish observational, comparative study (CUVA Study), adherence was significantly better in those patients with a once-daily therapy compared with those with a twice-daily regimen (50.2% and 43.5%, respectively reported appropriate adherence as indicated by a structured validated questionnaire).

However, using a once-daily regimen is not the only factor (nor perhaps the most important) affecting adherence, therefore other measures should not be ruled out. The previously quoted meta-analyses found adherence rates, even with once-daily regimens, which would be considered insufficient if applied to antiretroviral...
therapy. The use of once-daily regimens is one of several possible interventions and its impact depends on both individual factors and a number of external factors including pill burden, tolerance to drugs which make up the regimen, potency and efficacy, existence of resistance mutations, etc. (Level of evidence III).

Is once-daily dosing better adapted to patient lifestyle?

It is obvious that one dose can be more easily adapted to any lifestyle than more than one dose. In the CUVA study, satisfaction with the therapy was higher in patients receiving once-daily regimens (64.8% compared with 50.8%).

Nevertheless, there may be limitations if the regimen is conditioned by the time and method of dosing. These possible conditioning factors should be discussed with the patient on an individual basis in order to select the most adequate combination of drugs (Level of evidence IV).

Do patients ask for once-daily therapy?

Patients usually ask for their treatment to be simplified (reduced pill burden, reduced number of doses), although they generally do so without considering the real possibilities of their specific situation, and are occasionally conditioned by incomplete or inaccurate information transmitted by the media or by other patients. The preference of patients for once-daily regimens seems conditioned by pill burden (Level of evidence III). A study carried out among patients from different European countries showed a majority preference for a once-daily regimen when the number of pills to be taken was four or less, and that most patients preferred to divide treatment into two separate administrations when the number of pills was greater than six.

Does once-daily dosing improve patient quality of life?

The perception of quality of life is subjective and we attempt to quantify it by concentrating on the impact of the disease and its treatment on the different areas of the patient’s life, areas which involve a wide and global concept of health (social, psychological and physical function). An efficacious therapy which reduces or eliminates the symptoms is usually the most useful intervention in symptomatic patients.

The use of once-daily regimens can improve the perception of quality of life by its influence on the patient’s social sphere: it places fewer limitations on social and working activity and favours confidentiality by restricting administration to the patient’s private life (Level of evidence IV).

In any case, this influence will vary according to individual social and psychological circumstances and will depend on the tolerance to a specific regimen.

Is this option the most widely used by physicians?

Physicians appreciate the advantages of these regimens, but give priority to other aspects, such as potency and tolerance.

There has been a rapid increase in the use of once-daily regimens, stemming from both the growing number of drugs and combinations available for once-daily dosing, the wider experience gathered in clinical practice and from the many clinical trials in progress (Level of evidence IV).

### Table 5. Pharmacokinetic parameters of non-nucleoside analogues and protease inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>C_{max} (µg/mL)</th>
<th>C_{min} (µg/mL)</th>
<th>Plasma t_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>600 qd</td>
<td>4.1</td>
<td>1.8</td>
<td>40–55</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 bid</td>
<td>3.6–5.7</td>
<td>1.9–3.7</td>
<td>25–30</td>
</tr>
<tr>
<td>400 qd</td>
<td></td>
<td>4.5–6.7</td>
<td>1.1–2.9</td>
<td></td>
</tr>
<tr>
<td>Amprenavir/r</td>
<td>600/100 bid</td>
<td>5.15</td>
<td>1.51</td>
<td>7–10</td>
</tr>
<tr>
<td>1200/200 qd</td>
<td>7.75</td>
<td>1.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>400 qd</td>
<td>5.37</td>
<td>0.16</td>
<td>7.0</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>300/100 qd</td>
<td>5.23</td>
<td>0.86</td>
<td>8.6</td>
</tr>
<tr>
<td>400/100 qd</td>
<td>7.75</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir/r</td>
<td>700/100 bid</td>
<td>6.08</td>
<td>1.45</td>
<td>5.3</td>
</tr>
<tr>
<td>1400/200 qd</td>
<td>7.24</td>
<td>2.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir/r</td>
<td>1000/100 bid</td>
<td>3.88</td>
<td>0.45</td>
<td>2.7–3.2</td>
</tr>
<tr>
<td>1000/100 qd</td>
<td>8.6</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1200/400 qd</td>
<td>12.0</td>
<td>0.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800/200 qd</td>
<td>7.5</td>
<td>0.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saquinavir/r</td>
<td>1000/100 bid</td>
<td>2.7–4.3</td>
<td>0.37–0.48</td>
<td>3.6–4.5</td>
</tr>
<tr>
<td>1600/100 qd</td>
<td>1.54–8.0</td>
<td>0.07–0.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>400/100 qd</td>
<td>9.81</td>
<td>5.51</td>
<td>6</td>
</tr>
<tr>
<td>800/200 qd</td>
<td>10.94</td>
<td>2.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>1250 bid</td>
<td>3–4</td>
<td>1–3</td>
<td>3.5–5</td>
</tr>
</tbody>
</table>

qd, once daily; bid, twice daily; r, ritonavir.
is a group of drugs with a very long half-life (didanosine, emtricitabine, tenofovir, efavirenz and atazanavir) and another group (lamivudine, abacavir and boosted PIs) with a shorter half-life. The pharmacokinetics of zidovudine, stavudine, zalcitabine (ddC) and the non-boosted PIs (except atazanavir) do not support the possibility of using these drugs once daily.

Many situations in real life lead to forgotten or delayed doses, or even prolonged treatment interruptions. Discontinuing a regimen whose drugs have different half-lives may result in eventual monotherapy with the drug with the longest half-life. The use of three drugs with a long half-life could provide a pharmacokinetic advantage in case of delay or even forgetting the dose, as there is an additional margin of time during which the concentrations of the drug remain higher than necessary (Level of evidence IV). This phenomenon is known as the ‘forgiveness’ margin and is independent of whether the drug is administered once or twice a day. A recent study showed that when drugs with a long half-life are used, such as non-nucleoside analogues, the suspension of treatment for 48 h does not affect virological control or the appearance of resistance, whereas virological control can be lost if PIs with a shorter half-life are suspended for 2 days.104

In general, the administration of a whole daily dose at once leads to an increase in $C_{\text{max}}$ and a fall in $C_{\text{min}}$ compared with twice-daily dosing. The higher toxicity observed when some drugs (nevirapine, boosted PIs) are administered as once-daily regimens is due to a decrease in $C_{\text{min}}$.53,54 The reduction in $C_{\text{min}}$ may be important when boosted PIs are used in rescue therapy, since the virus presents reduced susceptibility to the drug. Reductions of up to 50% in the inhibitory quotient have been observed when a boosted PI is used in a once-daily regimen compared with the same dose twice daily.58,105

**Statement**

(1) At present, it is possible to design once-daily therapeutic regimens using some of the combinations of drugs considered as first choice in national and international recommendations for antiretroviral therapy (Grading of recommendation A).

(2) The efficacy and tolerability of therapy depend on the regimen chosen, regardless of its method of administration. Once-daily dosing is considered an added value which could favour adherence and, therefore, efficacy, as well as the quality of life of certain patients (Grading of recommendation C).

(3) Once-daily therapy may be useful in any therapeutic scenario, although the options for use are greater in the case of initial therapy and simplification of therapy in patients with a good therapeutic response to more complex regimens (Guiding of recommendation A).

(4) The objective of adequate adherence in the long term is often difficult to achieve regardless of the treatment used. The use of once-daily dosing could make maintenance of adherence easier (Guiding of recommendation B).

(5) In theory, any patient can receive once-daily therapy, although some patients could particularly benefit from it, e.g., those with unfavourable social or personal circumstances, including drug users, patients whose treatment must be supervised, patients receiving multiple medications, or those who need rescue therapy after multiple treatment failures (Guiding of recommendation C).

(6) At present, the options for antiretroviral combinations which can be administered once daily are still limited. The marketing of new drugs with this characteristic could allow us to increase the number and types of patient who can benefit from once-daily regimens, including those patients who need rescue therapy (Guiding of recommendation C).

(7) The selection of drugs whose pharmacokinetic characteristics best adapt to once-daily dosing (drugs with a longer half-life) could increase the total margin of tolerance to a delayed or missed dose, thus avoiding the negative repercussions on efficacy of therapy in these patients (Guiding of recommendation C).

**Acknowledgements**

The organization of the meetings was supported with an unrestricted grant from Bristol-Myers Squibb and RIS (Red Temática Cooperativa de Grupos de Investigación en SIDA del FIS).

**References**


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and lamivudine, as initial therapy for patients infected with HIV. *J Acquir Immune Defic Syndr* 2004; 36: 1011–9.


**Appendix: participants in the Spanish consensus on once-daily antiretroviral therapy**

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