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Abstract

Due to high inter-patient variability, and efficacy-concentration and toxicity-concentration relationships, optimization of HIV-protease inhibitor doses based on plasma concentrations could be beneficial. During a 48-week open prospective non-randomized interventional study of 115 protease inhibitor-naïve patients initiating an indinavir/ritonavir or lopinavir/ritonavir or nelfinavir containing therapy, protease inhibitor dose was modified when plasma trough concentrations (C_{trough}) at week 2, 8, 16 and 24 were outside predefined optimal concentration ranges. Failure of the strategy was defined as the proportions of patients with HIV-RNA above 200 copies/ml from week 24 to 48 and/or experiencing grade 2, 3 or 4 PI-related adverse events during the study; proportion of patients with last C_{trough} measurement outside the concentration range was determined at each visit. Virological failure and/or occurrence of adverse event were observed in 37/94 assessable patients (39% $CI_{95\%}$: 29.4–50.0). In the on-treatment analysis, failure of the strategy was noted in 16% of indinavir/r or lopinavir/r treated patients (8/51; $CI_{95\%}$ 7.0–28.6; virological failure: 2; adverse event: 6) but in 44% of nelfinavir-treated patients (11/25; $CI_{95\%}$: 24.4–65.1; virological failure: 10; adverse event: 1); C_{trough} concentrations outside the range were less frequent at the last measurement than at W2 (41% versus 66%; $p < 0.05$) with proportions of 35% for indinavir/r or lopinavir/r treated patients, but 57% for nelfinavir treated patients. The proposed strategy of therapeutic drug monitoring may be beneficial to indinavir/r and lopinavir/r-treated patients, but for nelfinavir failed to move concentrations into the predefined range and to produce the expected virological success.

MESH Keywords Adult ; Antiretroviral Therapy, Highly Active ; methods ; Dose-Response Relationship, Drug ; Drug Monitoring ; methods ; Drug Resistance, Viral ; Female ; Follow-Up Studies ; HIV Infections ; drug therapy ; HIV Protease Inhibitors ; adverse effects ; pharmacokinetics ; therapeutic use ; Humans ; Male ; Middle Aged ; Prospective Studies ; RNA, Viral ; metabolism ; Young Adult

Introduction

In HIV-infected patients, rapid achievement of undetectable HIV-RNA, which is noted in less than 75% of patients, has been linked to long-term favorable clinical prognosis (1 –3). It is thus desirable to increase the rate of early virological success. Improvement of adherence has proved to be of benefit in some patients (4). Occurrence of at least moderate severity adverse events is also frequent in protease inhibitor treated patients and reported in 15–20% of patients and may limit adherence (2 , 3 , 5). Due to high inter-patient variability and the efficacy-concentration and toxicity-concentration relationships, optimization of protease inhibitor doses based on plasma concentrations could be beneficial (6 –8).

Use of therapeutic drug monitoring to improve virological success and tolerance is approved in certain situations in the guidelines of some European countries as well as in US guidelines (9 , 10). These recommendations are based on observational data (8 , 11 , 12), rather than on experimental data (7 , 13 –15). In fact, the rare prospective studies evaluating feasibility and efficacy of therapeutic drug monitoring show conflicting results or demonstrated limited benefit (7 , 13 –18). However, the benefit of dose optimization may have been limited by the existence of drug resistance (as many of the patients were heavily antiretroviral therapy-experienced), or by target concentrations which were too low (7 , 14 , 15).

As the feasibility and the utility of therapeutic drug monitoring is still under debate, we conducted an open prospective non-randomized interventional study in protease inhibitor naïve patients, initiating one of the following protease inhibitors available for clinical use at the time of the study: indinavir/ritonavir (indinavir/r), lopinavir/ritonavir (lopinavir/r) or nelfinavir We then assessed the efficacy and the feasibility of protease inhibitor therapeutic drug monitoring in improving both virological efficacy and protease inhibitor tolerance. As most adverse events occur in the first weeks of protease inhibitor therapy (5), our goal was to modify protease inhibitor doses as early as possible to reduce the occurrence of these events, based on week 2 plasma level determinations.

Methods

Study design and patients

Cophar 2 -ANRS 111 was a prospective, multicenter, 48-week open study which was conducted between July 2003 and November 2004 in protease inhibitor naïve HIV-infected patients, and which evaluated the feasibility and the efficacy of therapeutic drug monitoring of protease inhibitors. The patients, recruited in 22 centres in France, were adults ≥ 18 years old, who had laboratory documentation of HIV-1 infection, a plasma HIV-1 RNA concentration above 1000 copies/ml within 4–6 weeks before entry, and no prior use of protease inhibitor containing therapy. For nucleoside analogue experienced patients, the baseline reverse transcriptase genotype had to present fewer than 2 major mutations among T215Y/F, Q151M, M184V/I, V75M/S, L74V with a genotype interpretation predicting more than 3 active nucleoside analogues based on genotypic interpretation with the French agency for research on AIDS (ANRS) AC-11 algorithm (version 11, September 2003) (www.hivfrenchresistance.org , connected February 2008) except for zalcitabine. Pregnant women, patients with acute HIV infection, and those with chronic diarrhea, diabetes mellitus, renal, liver or cardiac diseases or a history of nephrolithiasis could not be included. Patients taking rifampin, rifabutin or antiepileptic drugs were excluded at baseline and also during the study.

Eligible patients were prescribed a protease inhibitor containing antiviral therapy among the following combinations: indinavir/r (400 mg or 600 mg or 800 mg indinavir combined with 100 mg ritonavir, twice daily), or lopinavir/r (400 mg/100 mg, twice daily), or nelfinavir (2 tablets of the 625 mg formulation, twice daily), with an open choice of two analogues nucleosides reverse transcriptase inhibitors. The choice of protease inhibitor type and initial indinavir/r dose were left to physicians' discretion. Dietary guidelines, both oral and written, were given to all patients receiving nelfinavir recommending the ingestion of the pills with food containing a sufficient amount of fats.

Clinical and biological follow-up

Patients had clinical visits scheduled at screening, at inclusion and at weeks 2, 4, 8, 16, 24, 36 and 48. Standard biological exams were performed at screening and at each visit except week 2. CD4 cell count and plasma HIV-1-RNA (monitored Roche, limit of quantification of 50 copies/ml) were assessed at screening, and weeks 8, 16, 24, 36 and 48. Adherence was assessed through ANRS self-administered questionnaire, which was completed at weeks 2, 8, 16, 24 and 48 in the absence of the investigator in charge of the patients. Failure to take any dose of antiretroviral during the 4 preceding days was defined as non-adherence in this study.

Measurement of protease inhibitor drug concentrations

Protease inhibitor trough concentration (C_{trough}) was measured at week 2 before the morning protease inhibitor intake and was collected 12 ± 2 h after the intake of the preceding evening. Protease inhibitor C_{trough} concentrations were also systematically monitored at weeks 8, 24, 48 and 2 weeks after each dose modification.

Plasma concentrations were determined in each lab of the participating centres. These laboratories were cross-validated before starting the study. Results of the blind interlaboratory quality control at three concentrations for each protease inhibitor were within 15% of the target values for medium and high values and within 20% for low values.

Doses adaptations

Adequate C_{trough} therapeutic ranges were 150–550 ng/ml for indinavir, 2500–7000 ng/ml for lopinavir and 1500–5500 ng/ml for nelfinavir (without considering the M8 metabolite). From week 2 up until week 24, doses were modified whenever protease inhibitor C trough was out of recommended ranges according to a predefined algorithm. For indinavir and nelfinavir, therapeutic ranges were defined based on data from the literature analyzing the concentration–efficacy and concentration-tolerance relationship (8 , 11 , 12 , 19 –21). For lopinavir, as no such study existed, and as the inhibitory quotient with wild type virus is very high (above 75), it was hypothesized that the

25–75% interquartile range of the trough concentration observed in a population of protease inhibitor naive patients could be defined as a therapeutic range, which both maintained virological efficacy and decreases toxicity (22). For indinavir/r and lopinavir/r, modifications were introduced by increments of one pill twice daily (200 mg for indinavir, 133/33 for lopinavir/r). For nelfinavir, the increment was introduced using one pill of the 250 mg tablet formulation. If recommended based on week 2 results, protease inhibitor doses had to be adjusted at the week 4 visit by the clinician in charge of the patient following advice given by a centralized "pharmacological monitoring committee". In the absence of dose adjustments, the C_{trough} was monitored at week 8. Doses could further be modified after each planned C_{trough} determination up to the week 24 visit to achieve adequate concentration range according to plasma C_{trough} and the recommendations of the "pharmacological monitoring committee". After each dosage adjustment, the C_{trough} was monitored in the 2 weeks following modification. When the physician in charge of the patients or the "pharmacological monitoring committee" suspected non-adherence, importance of adherence was stressed to the patients in a counselling session and C_{trough} was monitored again before any dose modification. Patients were considered highly adherent if they declared having taken at least 90% of their PI doses during the 4 preceding days (12).

While 10 patients initially receiving nelfinavir (625 mg tablets formulation) experienced a virological failure at week 16, and because of the failure to achieve the predefined nelfinavir concentration range by adding tablets of 250 mg, the nelfinavir drug adaptation algorithm was modified by the "steering committee". Ritonavir 100 mg twice daily was systematically added for any patients with C_{trough} below 1500 ng/ml according to the preceding plasma level measurement and dose could be modified up to week 48 rather than week 24. Low doses of ritonavir, were supposed to increase nelfinavir plasma level by inhibiting nelfinavir catabolism.

Assessment of outcome

As this study was aimed at evaluating a strategy, we choose a composite criteria to define the failure of the strategy (23). Failure was defined as 1/two consecutive values plasma HIV-1 RNA levels above 200 copies/ml from week 16 to week 48 or 2/the occurrence of any protease inhibitor-related adverse event from inclusion to week 48, classified as severe (grade 4) or serious (grade 3), or any grade 2 diarrhea, nephrolithiasis or a total cholesterol level above 10 times the normal value, regardless of whether the adverse event led to the interruption of study medication or not.

Assessment of adverse events was based on a semi-directive questionnaire which included all possible adverse events, and on scheduled biological evaluation. At each clinical visit, patients were asked if they had had any clinical events possibly reflecting a drug adverse event. Each investigator in charge of the patient had to declare to the "Safety Committee" the suspected adverse event, regardless of its severity grade or its relationship to the treatment. This committee, blinded to drug plasma levels and protease inhibitor doses, scored the severity of the event and its relation to protease inhibitor using a standardized definition, and the toxicity grading scale of the ANRS. Adverse events were categorized as being either unrelated or possibly, probably or definitely related to treatment; these last 3 three situations thereafter were referred to as "related adverse event" (24). The primary outcome measure was the proportion of assessable patients for whom the strategy failed. Patients were considered as being assessable either if they had at least one available plasma HIV-RNA after week 16, or if the absence of plasma HIV-RNA was due to a protease inhibitor related adverse event prior to week 16.

For the secondary outcome, failure of the strategy was defined as the proportion of patients who had their last C_{trough} measurement outside the predefined concentration range.

Statistical analysis

The sample size of 100 assessable patients (33 patients in each arm), was calculated with the goal of establishing that the strategy failure rate was significantly lower than 30% with an overall type I error of 5%, a power of 80% and a two-sided z test. The rate of 30% was determined based on previous studies published in the literature which reported this rate of virological failure and/or severe (grade 4) adverse events (11 , 22 , 25 , 26), and on the assumption that therapeutic drug monitoring would decrease both the occurrence of protease inhibitor related adverse event and the rate of virological failure.

First, the proportions of failure, and its 95% confidence intervals were computed in all assessable patient as defined previously. Second, an on treatment analysis was performed including patients who did not interrupt study medication for other reasons than virological failure or protease inhibitor related adverse events.

For the secondary outcome on concentrations, we analyzed only patients with available trough concentration at the considered visit for the change in the proportion of patients with concentration outside the range between week 2 and the last concentration measurement was tested using a Mac Nemar χ^2 for paired data, in the sample of patients having at least two measurements including one at week 2. As the results of the strategy indicated a much poorer virological response in nelfinavir receiving patients as compared to those receiving indinavir/r and lopinavir/r, we decided to perform a post-hoc analysis in order to assess whether the failure rate was significantly lower than 30% in a group combining indinavir/r and lopinavir/r receiving patients. We also compared the rate of the last C_{trough} determination outside the therapeutic range of the nelfinavir group to those of the indinavir/r –lopinavir/r group.

Ethics

Written informed consent was obtained from all patients. The protocol was approved by the Kremlin Bicêtre Hospital Ethics Committee (Paris, France). An “independent committee” formed before the initiation of the study was in charge of monitoring the security of the study throughout its course.

Results

Characteristics of the study population and disposition of patients

Between July 2003 and November 2004, 130 patients underwent screening procedures, and 115 patients were included in the study. All patients were protease inhibitor naïve and 6 were nucleoside analogue experienced (3, 2 and 1 in the indinavir/r, lopinavir/r and nelfinavir groups respectively); 42 patients initiated an indinavir/r containing therapy (25 patients on 400 mg twice daily, 10 patients on 600 mg twice daily and 7 patients on 800 mg twice daily), 38 a lopinavir/r containing therapy, and 35 a nelfinavir containing therapy. Median baseline HIV-RNA was 5.5 $\log_{10}$ copies/ml (range 3.1–7.1), and median CD4 cell count was 167/mm^3 (range 10–980). Baseline patient characteristics according to the received protease inhibitor are displayed in Table 1 . Overall, 12 among the 42 indinavir/r-treated patients (29%) discontinued study medication and/or were excluded before week 16 for other reasons than a protease inhibitor related adverse event, as was the case for 6 out of the 38 lopinavir/r-treated patients (16%), and 3 out of the 35 nelfinavir-treated patients (9%)(Figure 1). The number of assessable patients was therefore 94: 30 indinavir/r-treated patients, 32 lopinavir/r-treated patients and 32 nelfinavir-treated patients.

Follow-up and study end points

In the analysis, in which assessable patients who interrupted study medication were classified as failure, the proportion of patients who failed the strategy was 37 out of the 94 assessable patients (39.4%; $CI_{95\%}$: 29.4–50.0), even higher than (although not significantly different from) the primary assumption of 30% of failures, without therapeutic drug monitoring. This result points to the failure of our treatment strategy. These 37 failures were composed of 18 patients who interrupted study medication for another reason than a virological failure or an adverse event, 12 patients with virological failure, and 7 patients with protease inhibitor related adverse events (Figure 1).

The 12 patients with virological failures were 1 indinavir/r treated patient, 1 lopinavir/r treated patients and 10 nelfinavir-treated patients. None of the patients experiencing a virological failure were nucleoside analogue experienced patients. The 7 patients with protease inhibitor related adverse events corresponded to 2 indinavir/r treated patients (2 nephrolithiasis, one at week 16, the other at week 46), 4 lopinavir/r treated patients (gastrointestinal adverse events in all occurring at day 3, week 2 week 2 and week 15, respectively), and 1 nelfinavir treated patient (diarrhea leading to drug interruption); of note is that 4 out of these 7 adverse events occurred before week 2, 2 out of the remaining 3 occurred in patients with adequate PI plasma levels. The rate of failure was significantly higher in the nelfinavir group (18/32 failures; failure rate of 56.3 %; $CI_{95\%}$: 37.7–73.6) than in the indinavir/r or lopinavir/r group (19/62 failures; failure rate of 30.6%; $CI_{95\%}$: 19.6–43.7) ($p<0.03$) (Table 2).

In the on treatment analysis, the strategy failed in 44% of the nelfinavir treated patients (11/25 failure; $CI_{95\%}$: 24.4–65.1), and in 16 % of the indinavir/r or lopinavir/r treated patients (8/51 failure; $CI_{95\%}$ 7.0–28.6, corresponding to 3 and 5 in the indinavir/r and lopinavir/r treated patients respectively); the rate of failure in the indinavir/r or lopinavir/r patients was significantly lower than 30% (Table 2).

Protease inhibitor concentrations at week two and during follow-up

C_{trough} was measured at week 2 in 40, 36, and 34 in patients receiving indinavir/r, lopinavir/r and nelfinavir respectively. At week 2, the median (range; coefficient of variability) indinavir, lopinavir and nelfinavir C_{trough} were 720 ng/ml (52–4670; 131%), 6700 ng/ml (200–19400; 81%), and 1330 ng/ml (68–3030; 60%) respectively. Overall, 56 % ($IC_{95\%}$: 47.1–65.7) of patients had C_{trough} outside the predefined concentration range; at week 2 this rate was 49% in indinavir/r-treated patients, 63% in lopinavir/r-treated patients and 56% in nelfinavir-treated patients and did not differ significantly between the 3 groups (Figure 2 , Table 3).

Considering all the concentrations observed during the 48 week follow-up, 57%, 69% and 84% of the patients receiving indinavir/r, lopinavir/r and nelfinavir respectively had at least one concentration falling outside the concentration ranges.. Among the 12 patients with virological failure, 8 (67%) including 7 in the nelfinavir group had concentrations below the therapeutic range at the time of the virological failure.

Over all, 45% of indinavir-treated patients, 67% of lopinavir-treated patients, and 76% of nelfinavir treated patients had at least one dose modification performed during the follow-up. In patients requiring dose modifications, 28%, 24% and 46% had more than 1 dose modification in indinavir/r, lopinavir/r and nelfinavir treated patients respectively. None of the patients receiving nelfinavir had his dose decreased during the study period. Among the patients receiving indinavir/r or lopinavir/r, 9 patients had only a dose increase, 13 patients

only a dose decrease. Five indinavir/r treated patients experienced a “yoyo effect”, as did 4 lopinavir/r-treated patients and 1 nelfinavir–treated patient.

The final twice daily administered indinavir/r doses were 200 mg/100 mg in 5 patients, 300 mg/100 mg in 1 patient, 400 mg/100 mg in 12 patients and 600 mg/100 mg in 12 patients; final twice daily administered lopinavir/r doses were 266 mg/66 mg in 11 patients, 400 mg/100 mg in 15 patients and 533 mg/133 mg in 6 patients; final twice daily administered nelfinavir doses were 1250 mg in 6 patients, 1500 mg in 9 patients, 1750 mg in 7 patients, 1250 mg with 100 mg ritonavir in 3 patients and 1500 mg with 100mg ritonavir in 7 patients.

When considering all the patients who had at least two concentration measurements including one at week 2, the rate of C_{trough} outside the therapeutic range decreased significantly ($p<0.05$) from week 2 (66/100 = 66%) to the last C_{trough} determination (41/100 = 41%). The rates of last C_{trough} determination outside the therapeutic ranges were significantly different ($p<0.04$) between the nelfinavir group (19/31 = 57%) and the indinavir/r or lopinavir/r treated patients (24/69 = 35%) ($p=0.03$). In the 10 nelfinavir receiving patients for whom low dose ritonavir was initiated, 6 reached the therapeutic range.

Adherence

At week 2, 26 indinavir/r treated patients, 29 lopinavir/r treated patients and 26 nelfinavir treated patients answered the adherence questionnaire: 58%, 72%, and 58% of patients receiving indinavir/r, lopinavir/r and nelfinavir respectively were considered highly adherent. This rate was not significantly different between the 3 groups. There was no correlation between adherence score at week 2 and week 2 plasma C_{trough} in any group.

Discussion

This study shows that the feasibility of therapeutic drug monitoring appears variable according to the type of protease inhibitor, and that it could probably partly explain the differences in efficacy observed among the different groups of patients.

Virological failure, which was one of our efficacy criteria, was in fact highly different among the 3 groups of patients. One virological failure occurred in each group of assessable patients receiving indinavir/r and lopinavir/r whereas 10 virological failures occurred in patients receiving nelfinavir, a number far above the acceptable limit. According to the protocol design, protease inhibitor doses had been decreased to prevent the occurrence of adverse events in patients with C_{trough} above the defined optimal range as early as week 4, i.e. before they reached undetectable HIV-1 RNA. It is noteworthy that of the 25 such patients (none of whom were receiving nelfinavir), 24 of the 25 nonetheless reached undetectable level at week 16 and maintained this status. In fact, in all nelfinavir receiving patients, the dose adaptations were always in the direction of an increase in nelfinavir doses, and cannot therefore reasonably be blamed for having induced a poor virological outcome.

As our objective, beyond decreasing virological failure, was also to prevent the occurrence of the maximum number of adverse events, which are known to influence patients’ quality of life and adherence to antiretrovirals (27), we also considered grade 2, 3 and 4 adverse events to be a failure of our strategy, even if adverse events’ grade below 4 are generally not taken into consideration as judgment criteria in clinical trials. Even using this strict definition of failure and even given repeated active research of their occurrence through a semi-directive questionnaire, the rate of protease inhibitor related adverse events was below the reported rates of 15–25 % (2 , 3), we presume as a result of our strategy. Of note is that 4 out of the 7 adverse events occurred before week 2, i. e. before the first C_{trough} measurement; these not only could not have been prevented by our intervention, but perhaps should not even be counted as cases of strategy failure.

Even considering these large composite judgement criteria of failure, (virological failure and any grade 2, 3, 4 adverse events), our strategy appears to have been effective in indinavir/r and lopinavir/r treated patients, whereas it failed in nelfinavir receiving patients. However, we acknowledge that the interpretation of the present study is limited by the comparison of results to historical data without using a comparative arm in the study. Many factors may have had an impact on the comparison to historical data, such as the levels of immunodepression or of viral replication. However, these differences in efficacy among the three groups of treatment are concordant with the differences in success rate of concentrations reaching predefined therapeutic range between indinavir/r and lopinavir/r group and nelfinavir group. In fact, the significant decrease in the rate of patients with inadequate plasma level in indinavir/r and lopinavir/r treated patients due to dose adjustments was not observed in nelfinavir treated patients. In the latter patients, the algorithm initially used, without ritonavir, was not effective in raising the concentration into the targeted concentration range; this could be related to a reduced absorption of nelfinavir despite food recommendations which could not be counterbalanced by the increase of nelfinavir dose, or to the autoinductive effect of nelfinavir on its own metabolism leading to an increase catabolism of the drug when doses were increased (28). We can wonder to what extent the use of the 625 mg formulation of nelfinavir (Roche, tablets of 625 mg) might be responsible for these poor results. This is difficult to determine as only bioequivalence studies have been carried out (29). Another hypothesis could be that the combined use of the 625 mg and the 250 mg formulation of nelfinavir in patients for whom dose modifications were needed may have confused the patients in taking their medication. In all groups of patients, therapeutic drug monitoring led to modifying protease inhibitor doses in a large

number of patients, and resulted in protease inhibitor doses which were highly different among the patients, and in many patients different from what had been recommended in the protease inhibitor package insert. The question of the amount of fat ingested by the patients must also be addressed. All nelfinavir treated patients received written advice concerning the necessity to ingest a sufficient amount of fat at each nelfinavir intake. However, while we advised dietary improvement in some patients, we had no means of directly evaluating whether low concentrations were due to low absorption resulting from insufficient fat intake or due to patients' PK characteristics. We cannot rule out that the patients, despite dietary advice and monitoring by the practitioner, did not ingest sufficient amounts of fat. It is in fact highly difficult to precisely monitor fat intake in ambulatory patients. Interestingly, most of the patients for whom we did not succeed in reaching therapeutic range were those not initially receiving ritonavir as booster. After several unsuccessful attempts using only nelfinavir, we were able to achieve our goal only through boosting with ritonavir. We can hypothesize that the virological results would have been even less successful without this protocol modification.

The week 2 plasma level determination appeared to us a reasonable compromise allowing us to modify protease inhibitor dose as early as possible to reduce the occurrence of these events, but not so early as to precede stabilisation of patient plasma concentrations. It has been reported that a high intraindividual variability in protease inhibitor pharmacokinetic may limit the clinical utility of therapeutic drug monitoring, particularly when the decision is based solely on a single plasma determination (30). However, the goal of early intervention of the present study led us to base dose modification on a single plasma determination, i.e. without waiting for confirmation through a second measurement. This decision may explain why 10 patients presented a "yoyo effect": a patient falling above the predefined range limits, for whom dosage was therefore decreased, fell below range limits at the next monitored sample (and vice-versa). However, the statistically significant decrease in the rate of indinavir/r and lopinavir/r receiving patients outside the predefined therapeutic range as time went on seems to prove that therapeutic drug monitoring is effective in the conditions of our trial for patients receiving indinavir/r and lopinavir/r, despite using only one single plasma determination. Furthermore, it is not proven that a second plasma level determination would have prevented the yoyo effect and/or increase the strategy success. A precise determination of adherence as can be done using medication event monitoring system may have helped in interpreting the plasma level results and adapting protease inhibitor doses.

We acknowledge that our study has several limitations. First, it was a non comparative study which cannot prove the effectiveness of our strategy. Second, we did not perform any cost effectiveness analysis. Third, the rate of patients within a therapeutic range is highly dependent on the breadth of the range chosen. However, we feel that the critical information provided by one study is not the percentage of patients within the optimal range at the beginning but the increase following intervention. Fourth, our chosen lower range limit is higher than that reported by some authors. However, final doses received by some patients were much lower than those usually prescribed, and nevertheless did not induce virological failure. Fifth, indinavir and nelfinavir are two protease inhibitors which are no longer widely used. However, indinavir is currently always used when high CNS and genital compartment penetration is necessary. Last, drug-food interactions may have contributed to the observed variability in nelfinavir and lopinavir/ritonavir plasma concentrations. Such interaction may not be as great with the widespread use of the new lopinavir/ritonavir tablet formulation.

Conclusion

Our study shows that in protease inhibitor naïve patients without any drug resistance receiving indinavir/r or lopinavir/r, early therapeutic drug monitoring in our evaluated conditions increases the number of patients with adequate plasma concentration and seems to optimise both virological success and tolerance. Success of therapeutic drug monitoring appears dependant on the type of protease inhibitor evaluated. Results of this study may prove helpful in designing trials evaluating the benefit of therapeutic drug monitoring in HIV-infected patients.

Ackowledgements:

The authors thank the study participants and the participating clinicians at each site, Agence Nationale de Recherche sur le SIDA (ANRS, Essai 111) for financial support, and Roche for providing nelfinavir, Dr Agnes Certain for organizing the drug supply to all centers

Financial support: Agence Nationale de Recherche sur le SIDA (ANRS 111). Roche provided viracept.

APPENDIX

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Monitoring center: S. Auleley, E. Marcault, F. Mentré.

Statistics : E. Bouguen, F. Mentré. X. Panhard,

Footnotes:

Written Informed consent was obtained from all the patients. The study protocol was approved by the Kremlin Bicètre Ethics Committee, Paris, France.

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Figure 1

Profile of patient enrolment and discontinuation of study medication through week 48. AE: adverse event; IDV: indinavir/r; LPV: lopinavir; NFV: nelfinavir * for other reasons that a protease inhibitor-related adverse event $ 1 withdrew consent, 5 because of protease inhibitor non related adverse events, 3 because of AIDS defining event, 2 were lost to follow-up, 1 had baseline indinavir-genotypic resistant virus µ 2 for unallowed treatment, 2 because of AIDS defining event, 2 were lost to follow-up £ 1 withdrew consent, 1 because of adverse events, 1 because of unallowed treatment § adverse events occurred before week 2 in 3 patients of lopinavir/r group and in 1 patient of nelfinavir group ** adverse events not related to protease inhibitor

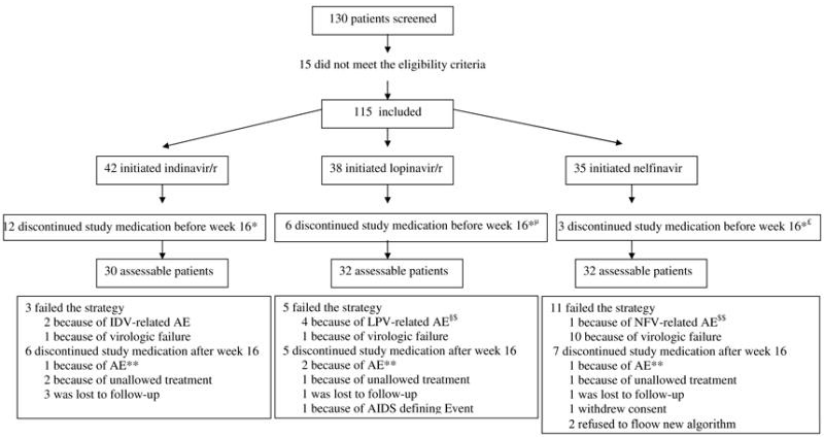
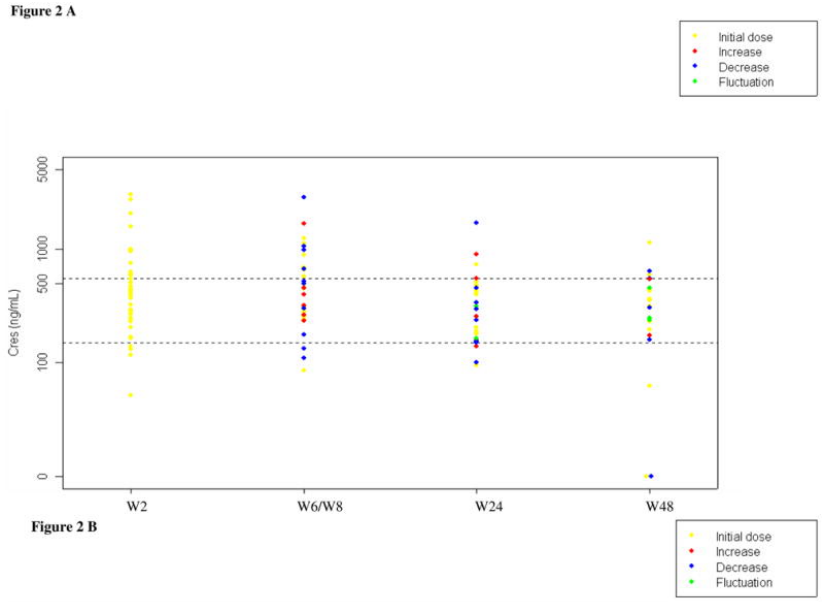
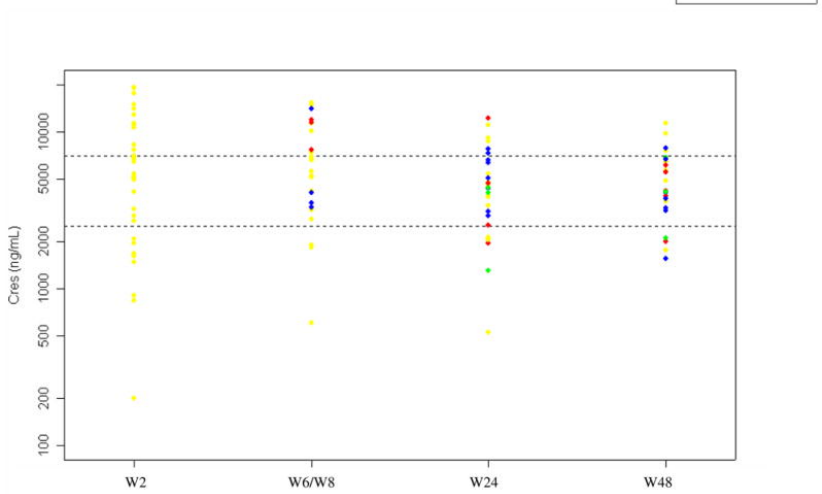


Figure 2

Protease inhibitor trough plasma concentrations and percentages of concentrations within the predefined ranges (doted lines) during the trial (A: indinavir; B: lopinavir; C: nelfinavir).





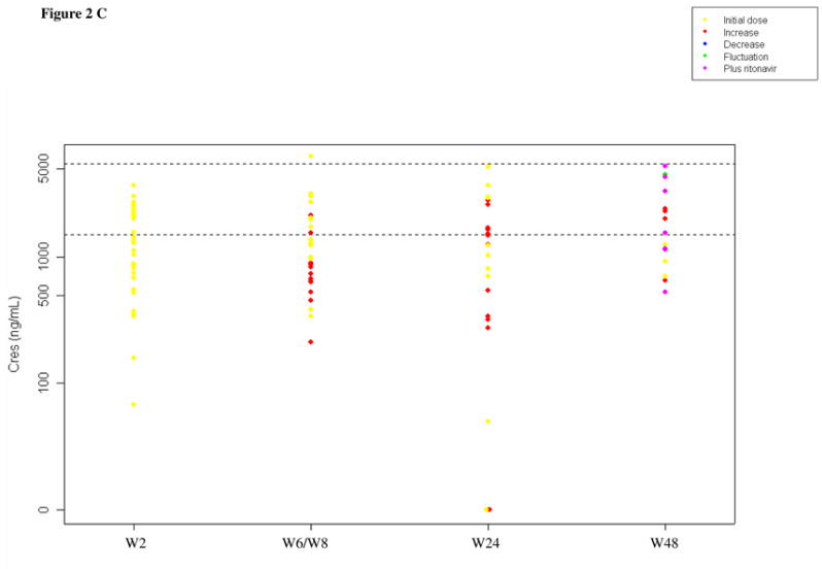


Table 1

Baseline characteristics of the 115 patients included in the Cophar 2-ANRS 111 study according to the protease inhibitor initiated.

	Indinavir/r	Lopinavir/r	Nelfinavir	Total
Patients (n)	42	38	35	115
Age, median [range]	37 [21–59]	39 [23–56]	35 [19–63]	37 [19–63]
Male (%)	66%	71%	43%	61%
CDC stage C (%)	26%	34%	14%	25%
ARV naïve* (%)	92%	95%	97%	95%
HIV-RNA $\log_{10}$ copies/ml, median [range]	5.3 [3.1–6.2]	5.3 [3.5–7.1]	5.6 [3.1–6.7]	5.5 [3.1–7.1]
CD4/mm^3, median [range]	210 [10–980]	144 [5–442]	142 [1–466]	167 [1–980]
HBs Ag or HCV antibodies (%)	14%	11%	6%	10%

Note:
CDC: Center for Disease Control
ARV: antiretroviral
* All patients were protease inhibitor naïve

Table 2

Trough protease inhibitor concentration, in protease inhibitor-naïve patients initiating a protease inhibitor-containing therapy and having C trough determination at the considering visit.

	Indinavir/r	Lopinavir/r	Nelfinavir
Trough plasma protease inhibitor concentration (C_{trough}*)			
Week 2			
Patients outside the range, % (N/total)	**50% (20/40)**	**64% (23/36)**	**56% (19/34)**
% below/% above the range	15%/34%	24%/39%	56%/0%
Week 6 or 8			
Patients outside the range, % (N/total)	**44% (15/34)**	**47% (15/32)**	**70% (21/30)**
Week 24			
Patients outside the range, % (N/total)	**22% (6/27)**	**41% (12/29)**	**56% (14/25)**
Week 48			
Patients outside the range, % (N/total)	**25% (5/20)**	**31% (8/26)**	**44% (7/16)**

Note:
* Optimal C_{trough} ranges were 150–550 ng/ml for indinavir, 2500–7000 ng/ml for lopinavir and 1500–5500 ng/ml for nelfinavir (without considering the M8 metabolite).

Table 3

Numbers of protease inhibitor related adverse events and virological failures in assessable protease inhibitor-naïve patients on a protease inhibitor-containing therapy.

	Indinavir/r	Lopinavir/r	Nelfinavir
Protease inhibitor related adverse effect, % (N /total*)	**7 % (2/30)**	**12 % (4/32)**	**3% (1/32)**
Before week 2	1	3	1
After week 2$	1	1	0
Virological failure, % (N µ /total)	**3 % (1/30)**	**3% (1/32)**	**31 % (10/32)**

Note:

* In assessable patients

$ Protease inhibitor doses could only be modified at or after week 4

μ Assessable patients with HIV-RNA above 200 copies/ml at 2 consecutive determinations at 15 days apart after week 16;