Antiretroviral Drug Dosing Errors in HIV-Infected Patients Undergoing Hemodialysis

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Background. Several studies have revealed the frequency of antiretroviral (ARV) drug prescription errors. We analyzed highly active antiretroviral therapy (HAART) prescribing practices for human immunodeficiency virus (HIV)–infected patients undergoing hemodialysis in France.

Methods. Prescribed ARV drug doses in our cohort (consisting of all HIV-infected patients who underwent hemodialysis from 1 January 2002 and were prospectively followed up until 1 January 2004) were compared with the recommended doses for patients undergoing hemodialysis. The log-rank test was used to compare the outcomes among different groups of treated patients.

Results. One hundred seven of the 129 patients in our cohort received a total of 317 ARV drugs, 59% of which were improperly prescribed. The dosing was too low for 18% of the patients and too high for 39% of the patients. Twenty-eight patients (26%) did not receive any of their ARV drugs at the recommended dose. The lowest prescribed dose (8% of the daily recommended dose) was observed with indinavir and zidovudine, and the highest prescribed dose (1000% of the recommended dose) was observed with stavudine. Among patients who received HAART, those who were prescribed an insufficient dose of a protease inhibitor had more-severe HIV disease and worse 2-year survival than did the other patients (mean rate of survival ± standard deviation, 79.5% ± 7.5% vs. 95.4% ± 2.6%, respectively; $P < .02$). For dialyzable ARV drugs, the delay between ARV drug receipt by the patients and dialysis sessions was not respected in 9% of cases, and in 73% of cases, it was not known whether the patients took the ARV drugs before or after dialysis sessions.

Conclusion. This is, to our knowledge, the first study to show a significant association between ARV drug prescription errors and survival in patients undergoing dialysis.

Antiretroviral (ARV) medications have revolutionized HIV-infected patients' prognosis. Despite the numerous beneficial effects of ARV therapy, new problems have emerged, such as patients' poor adherence to their regimen, virus resistance, drug interactions, and drug-related adverse effects. HIV-infected patients also live longer, and complications now arise that patients once did not have time to develop (e.g., heart disease, hypertension, osteoporosis, hepatic, and abnormal renal function). Therefore, ARV drug prescription has become increasingly complex, leading to a certain number of prescription errors. Purdy et al. [1] studied 108 ARV drug prescription errors that occurred among HIV-infected patients hospitalized from 1996 through 1998. The rate of error increased from 2% of hospital admissions in 1996 to 12% in 1998, as 2 new classes of ARV drugs became available: nonnucleoside reverse-transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). The most common errors were overdosing and underdosing of ARV drugs.

ARV drug prescription errors have also been shown to occur among outpatients. DeLorenze et al. [2] studied ARV drug prescriptions provided to 5473 HIV-infected outpatients. The incidence of confirmed dosing errors was 9.8 errors per 1000 new prescriptions. Patients aged >50 years were at a higher risk of receiving an erroneous dose, compared with patients aged <40 years (OR, 1.94).

Recently, Rastegar et al. [3] revealed that ARV medication errors occurred for approximately one-quarter

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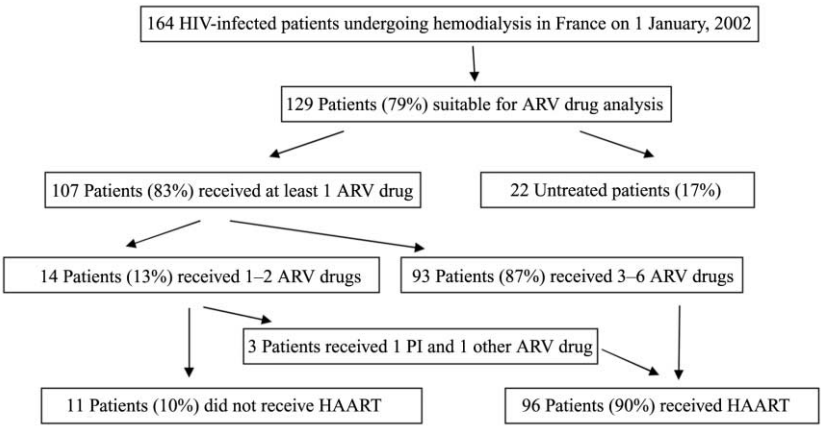

Figure 1. Repartition of patients in the French Dialysis in HIV/AIDS cohort. ARV, antiretroviral; PI, protease inhibitor.

of HIV-infected hospitalized patients. The most frequent error was incorrect dosing of ARV drugs, which was found for 16% of the total hospital admissions. Inadequate dosing for patients with chronic kidney disease (CKD), especially patients undergoing hemodialysis, occurred for 8% of the total hospital admissions. The authors intuited that these incidents might result in serious adverse events, such as toxicity, viral resistance, or treatment inefficacy, but they did not specifically study the impact of inadequate dosing on patient outcome. We used the French Dialysis in HIV/AIDS (DIVA) cohort to study the impact of ARV drug dosing errors on survival of HIV-infected patients undergoing hemodialysis.

MATERIALS AND METHODS

Patients. The DIVA prospective cohort has been described elsewhere [4, 5]. Essentially, all of the HIV-infected patients who underwent hemodialysis in France on 1 January 2002 were included. Subsequently, a questionnaire was sent to the nephrologists in charge of each of these patients. This form included 45 items, covering demographic, clinical, nephrologic, immunologic, and therapeutic characteristics. For all of the fluctuating data, the value we requested was that from December 2002 or the last available data before death (for patients who died before December 2002). For ARV treatment, the information we requested was in reference to the treatment that had been prescribed for the longest period in 2002. For each drug, the daily dose and frequency of administrations were requested. Furthermore, for the days when the patient was undergoing dialysis, the duration between dialysis sessions and receipt of ARV treatment was requested. To conclude this collection of information, a final survey was performed, requesting the living status (i.e., whether they were dead or alive) of the patients on 1 January 2004. In this study, HAART was defined as (1) a treatment regimen containing at least 3 drugs, whether the regimen included a PI and/or an NNRTI, or (2) any regimen containing a PI.

ARV drug dosing in patients undergoing hemodialysis. For each ARV drug administered to patients in the DIVA cohort, the prescribed dose was compared with the daily recommended dose (DRD) for patients undergoing hemodialysis, as described in the literature [6, 7]. For this purpose, we used data from Information Counselling on Renal Adaptation (ICAR). ICAR is a service that delivers recommendations to French physicians for drug dosage adjustment for patients with CKD; these recommendations are based on a systematic review of the international literature. For the most recurrent questions, ICAR published a series of prescription handbooks, including a volume on antiviral therapy, in France [8] and in the United States [9]. These handbooks contain information that is consistent with the most extensive reviews on this topic [6, 7].

Statistical analysis. Data are given as mean ($\pm$SD) or number (%) of patients. Patients were divided into several groups, according to the characteristics of their ARV regimen. The Kaplan-Meier estimate of survival was calculated. Patients withdrawn from hemodialysis (because of renal function recovery or kidney transplantation) were censored. Survival time was calculated from 1 January 2002 to the date of death (or the date when the data were censored). The log-rank test was used to assess survival differences among the different groups of patients. All analyses were 2-tailed and performed using SAS, version 8.1 (SAS Institute). $P < .05$ was considered to be statistically significant.

RESULTS

Description of the study population. As previously described, there were 27,577 patients undergoing hemodialysis in France on 1 January 2002, of whom 164 were infected with HIV (figure 1). These patients formed the DIVA cohort [5]. All patients

were cared for by both a nephrologist and an infectious diseases (ID) specialist. For all of the patients, ARV treatment was initiated or modified by the ID specialist only.

No information was available for 24 patients. These patients were declared as HIV-infected patients undergoing hemodialysis on 1 January 2002 (inclusion survey); however, their questionnaire was never returned (December 2002). For 2 patients, data were missing on the dosing of the prescribed ARV drugs. For 3 patients, all data were available; however, the living status as of 1 January 2004 was not provided. In the end, ARV treatment and clinical data were fully detailed by the nephrologists for 135 patients (82% of the total patients). Five patients who received amprenavir therapy and 1 patient who received emfuvirtide therapy were excluded, because there are no available data for amprenavir or emfuvirtide use in patients undergoing dialysis. Of the remaining 129 patients, 107 (83%) were prescribed at least 1 ARV drug. Treated patients were prescribed a total of 317 ARV drugs (mean, 3 ARV drugs per patient). Fourteen patients (13% of the treated patients) received 1 or 2 ARV drugs, 93 patients (87%) received 3–6 ARV drugs, and 96 patients (90%) received HAART. Among the patients who received HAART, 70% received at least 1 PI and 30% received at least 1 NNRTI. Three patients treated with HAART received only 2 ARV drugs. One was treated with efavirenz and nelfinavir, 1 with stavudine and nelfinavir, and 1 with lamivudine and indinavir.

General prescription errors. Overall, 18% of the ARV drugs were prescribed at an insufficient dose, 39% were prescribed at a higher dose than was required, and 2% of the drugs were contraindicated for patients undergoing hemodialysis at the time of the study (i.e., amprenavir and enfuvirtide), resulting in a total of 59% of ARV drugs being improperly prescribed, according to existing recommendations for patients undergoing hemodialysis at the time of the study. Only 10 (9%) of the treated patients in the DIVA cohort were prescribed the appropriate dose of all of their prescribed ARV drugs, and 28 patients (26%) did not receive any of their ARV drugs at the recommended dose. Overall, treated patients received a mean number of 1.69 ± 0.95 ARV drugs at unconventional doses.

Prescription details. Figure 2 shows the most frequently over- and underprescribed drugs in the DIVA cohort. The highest overprescription was observed with stavudine. This drug was prescribed to 46% of the treated patients, and the dosing was too high in 61% of them. The highest prescribed dose was 10-times higher than recommended. Lamivudine was the most frequently prescribed ARV drug (administered to 74% of the treated patients). It was overprescribed in 62% of the cases. The maximum dose was 6-times higher than the DRD, and overall, patients receiving lamivudine were prescribed a mean dose that was 4.1 ± 1.8–times higher than the DRD.

Conversely, underprescription was more frequently observed

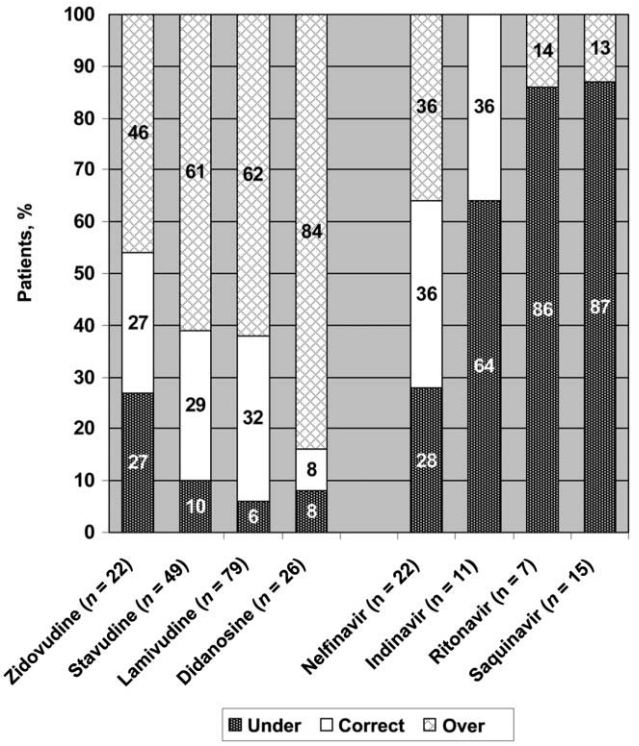

Figure 2. Details about the most frequently over- and underprescribed antiretroviral drugs. The *n* values represent the number of patients who received the drug (of 107 treated patients). Correct, patients who were prescribed the recommended dose for patients undergoing hemodialysis; over, patients receiving an overprescription of the drug; under, patients receiving an underprescription of the drug.

with PIs. Saquinavir was prescribed to 14% of the treated patients and was underprescribed for 87% of them. The lowest prescribed dose was 22% of the DRD, and overall, patients treated with saquinavir were prescribed a dose that was 59% ± 19% of the DRD. Indinavir was prescribed to 10% of the patients. The prescribed dose was inferior to recommendations for 64% of the patients. The lowest prescribed dose was 8% of the DRD, and overall, patients treated with indinavir were prescribed a dose that was 34.4% ± 20.1% of the DRD. NNRTI prescription errors were detected only for 2 patients.

Inadequate delay between dialysis sessions and ARV drug receipt. For each dialyzable ARV drug (i.e., didanosine, stavudine, lamivudine, zalcitabine, tenofovir, nevirapine, and nelfinavir), the nephrologists were asked to record whether the drug was administered before or after each dialysis session. The delay between ARV receipt and dialysis sessions was considered to be correct if the ARV was prescribed to be received after the dialysis sessions on dialysis days. It was considered to be erroneous if the nephrologist declared that the drug was to be received before the dialysis sessions. When the nephrologist did not respond to the question, the answer was considered to be unknown. A total of 209 ARV drugs were dialyzable (66% of

the total prescribed ARV drugs). The delay was correct for 18% of the drugs, erroneous for 9%, and unknown for the remaining 73%.

Influence of ARV drug underprescription on 2-year survival. Untreated patients in the DIVA cohort formed a very heterogeneous group. It consisted of very immunodepressed patients whose ARV indication was clear, but who refused any ARV treatment (7 patients with a mean CD4 cell count of 120 ± 75 cells/mm^3) and of patients with spontaneously elevated CD4 cell counts (15 patients with a mean CD4 cell count of 479 ± 228 cells/mm^3). Therefore, these patients were excluded from the survival analyses, which were performed for treated patients only.

Patients in the DIVA cohort who received HAART had a better 2-year survival rate than did patients who did not receive HAART (mean 2-year survival rate, 90.5% ± 3.0% vs. 63.65% ± 14.5%; $P < .005$) (figure 3). Among the patients who received HAART, those who were prescribed an insufficient dose of a PI were not statistically distinguishable from the others in terms of age, sex, ethnicity, diabetic comorbidity, HIV-associated nephropathy diagnosis, hepatitis B virus and/or hepatitis C virus coinfections, duration of dialysis, and duration of HIV infection. However, compared with patients who did not receive an insufficient dose of a PI, patients who received an insufficient dose had more-severe HIV disease, which was characterized by a higher mean viral load (2.9 ± 1.3 log copies/mL vs. 2.2 ± 0.9 log copies/mL; $P < .005$), a higher rate of AIDS (57% vs. 27%; $P < .006$), and a nonsignificant trend to have a lower mean CD4 cell count (271 ± 149 cells/mm^3 vs. 345 ± 188 cells/mm^3; $P < .06$) (table 1). Eventually, patients who received an underprescription of a PI had a poorer 2-year survival rate than did the other HAART-treated patients (mean 2-year survival rate, 79.5% ± 7.5% vs. 95.4% ± 2.6%; $P < .02$) (figure 4).

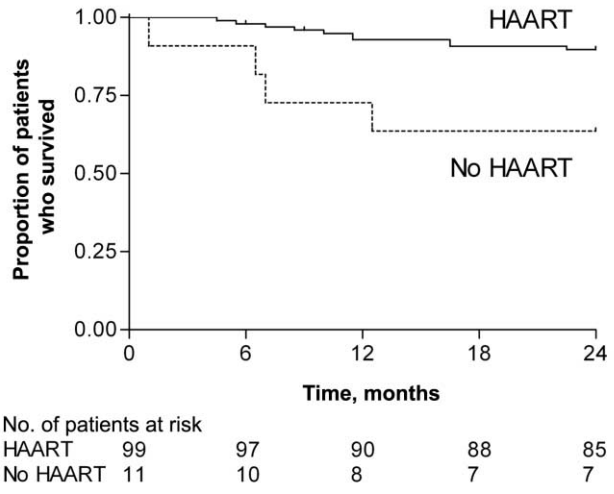

Figure 3. Kaplan-Meier survival curves of treated patients who received and did not receive HAART ($P < .005$).

Table 1. Characteristics of HIV disease in patients who received HAART with or without underprescription of a protease inhibitor (PI).

Characteristic	PI underprescription		*P*
	No	Yes	
CD4 cell count, cells/mm^3	345 ± 188	271 ± 149	NS
AIDS, % of patients	27	57	<.006
Viral load, log copies/mL	2.2 ± 0.9	2.9 ± 1.3	<.005
2-year mortality, %	95.4 ± 2.6	79.5 ± 7.5	<.02

NOTE. Data are mean ± SD, unless otherwise indicated. NS, not significant ($P < .06$).

Conversely, the survival of patients who received an underprescription of a nucleoside reverse-transcriptase inhibitor did not differ from the survival of the other treated patients. NNRTI prescription errors were detected only for 2 patients (the prescription indicated receipt of 200 mg of nevirapine once daily instead of twice daily). Their survival could not be statistically compared with that of the other treated patients.

DISCUSSION

In this study, we revealed that, among HIV-infected patients undergoing hemodialysis in France, ARV drugs are frequently misprescribed (in more than one-half of the cases). There are several possible explanations for this fact. First, ARV drug prescription requires very specific knowledge and training. It is generally restricted to ID specialists. New drugs constantly emerge—maybe more rapidly than in other fields of medicine. Numerous interactions exist between ARV drugs and between ARV drugs and other drugs. In addition to this intrinsic difficulty of ARV drug prescription, it is important to consider the dosing adjustment rules for patients with CKD. Some ARV drugs require dosing adaptation (e.g., nucleoside reverse-transcriptase inhibitors, except for abacavir), and others do not require dosing adaptation (e.g., NNRTIs and PIs) [6, 7]. As a result, there is a high risk of errors associated with ARV drug prescription for patients undergoing hemodialysis.

One possible theoretical bias might arise from the fact that ARV treatments were always initiated or modified by the ID specialists, and the questionnaires were sent to the nephrologists. Therefore, it is possible that, in some cases, the errors were not in the prescriptions but in reporting the patients' ARV drug regimens. However, we do not think that this occurred very frequently. As a matter of a fact, the treatments in all cases were initiated or modified by the ID specialist; however, the

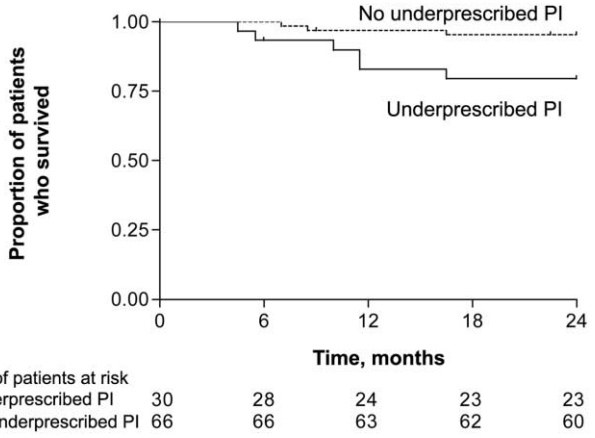

Figure 4. Kaplan-Meier survival curves for patients who received HAART with or without underprescription of a protease inhibitor (PI; $P < .02$).

patients presented to their nephrologist much more frequently than they did to their ID specialist. Because of this, the nephrologists frequently renewed the ARV drug prescriptions and were the main prescribers in a majority of cases. Another point is that no aberrant declarations in relation to patient treatments were found (e.g., impossible dosing for a drug, such as administration of 50 mg of the agent daily for a drug that exists only as 40-mg pills).

In this study, we demonstrate that overprescription occurs particularly frequently with nucleoside reverse-transcriptase inhibitors. At least in some cases, this is probably because of the fact that drug adjustment rules for patients undergoing dialysis are not respected. This is obvious in the case of lamivudine: 74% of the patients were prescribed this drug, and 62% of the treated patients received an overprescription. Among these overtreated patients, 44% received 300 mg of lamivudine per day, which is the regular dose for patients who do not have CKD, instead of the recommended dosage of 25–50 mg/day for patients undergoing hemodialysis. The same phenomenon was observed with zidovudine.

In contrast, PIs were frequently underprescribed. This is harder to explain. It might be the effect of an intuitive empirical dose adaptation caused by the erroneous thought that a PI dose adaptation is necessary. In the end, some prescriptions are made without consideration of nucleoside reverse-transcriptase inhibitor dosing adjustment rules and result in overprescription, and other prescriptions are made with an empirical decrease of PI dosing and result in underprescription.

We also show that patients who receive HAART have a better survival rate than do the other treated patients. This confirms that HAART is effective in patients undergoing hemodialysis. Although this has already been shown by Ahuja et al. [10], we believe that this result is worth emphasizing, because in the DIVA cohort, 10% of the treated patients still did not receive a HAART regimen. More interestingly, we show that patients who receive HAART with underprescription of a PI have more-severe HIV disease and a worse survival rate, compared with the others. A probable explanation to this result is that, when the PI is insufficiently prescribed, the patients are not treated with HAART but with a suboptimal therapy. This results in increased HIV replication, which we have previously shown to be an independent mortality factor among HIV-infected patients undergoing hemodialysis [5]. Our study is the first to show a significant link between inadequate treatment prescriptions and survival reduction. Our results are consistent with those of the recent study of ARV drug prescription errors by Rastegar et al. [3]. The authors showed that ARV drug prescription errors occurred frequently (for approximately one-quarter of hospitalized HIV-infected patients) and that a great source of error was dosing inadequacy with regard to renal status. Rastegar and colleagues intuited that these errors might have several deleterious effects. They specified that their study did not provide outcome data for the patients. In our study, we show that, in the specific context of HIV-infected patients undergoing hemodialysis, the impact of ARV drug dosing errors is dramatic, because it is a risk factor for death

Most of the recommendations with regard to drug adaptation in specific groups of patients (e.g., elderly patients, children, obese patients, and patients with CKD or liver diseases) are based on pharmacokinetics. It is very arduous to conceive randomized trials of dose adaptation in every subgroup of patients because of, for example, the insufficient number of patients to reach statistical significance and cost of the studies. In the context of ARV treatment for patients undergoing hemodialysis, dose adaptation recommendations are very often based on pharmacokinetic studies involving a few patients, if not only 1 patient. Therefore, our study strongly supports the international recommendations made for patients undergoing hemodialysis, because it shows that patients whose treatment is in accordance with these recommendations survive longer.

We also believe that our study highlights the importance of dosing adaptation counseling. In our department, ICAR was created in 1999. Any nephrologist and ID specialist in France can present questions in reference to dosage adjustment, according to the renal function of the patient, for any drug the doctor intends to prescribe. Within 24 h, ICAR counselors search international literature and pharmacological databases to provide the best dosing adaptation, also taking into account any potential interactions between drugs. In 2006, ICAR provided 1995 answers for 1050 patients. In our study, we show that this kind of counseling seems to be effective in increasing patients' survival in the specific context of ARV drug dosing adaptation for HIV-infected patients undergoing hemodialysis.

Lastly, we demonstrated that, for drugs that specifically needed to be received after dialysis sessions, the delay between

dialysis sessions and drug receipt was unknown in the vast majority of the cases (73%). This implies that patients were free to decide when to take their treatment on dialysis days. Depending on the schedule of the dialysis sessions, it is likely that ARV drugs were mistakenly absorbed before dialysis sessions in a certain number of cases. This could result in treatment inefficiency because of dialysis drug clearance.

Although it is hard to admit, prescription errors are unavoidable. Every action must be carefully considered to minimize this risk and its consequences to the patient. ARV drugs are frequently misprescribed for HIV-infected patients undergoing hemodialysis, probably because it requires the specific knowledge of both the nephrologist and the ID specialist. We think that it is of paramount importance that physicians who actually prescribe ARV treatment to patients with CKD are aware of the necessary drug dosing adjustment, because the survival of their patients may depend on it.

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