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Evaluation of clinical pharmacist interventions on drug interactions in outpatient pharmaceutical HIV-care

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SUMMARY

Objective: **To evaluate the usefulness of intervention in drug interactions of antiretroviral drugs with coadministered agents by a clinical pharmacist in outpatient HIV-treatment.**

Methods: **The study design included two intervention arms (A and B), which were both preceded by a control observation period. In arm A, a complete list of the currently used drugs, extracted from pharmacy records was provided to the treating physician. In arm B the same list was provided but with a notification when a drug interaction was present and an advice how to handle this. The infectious disease specialist obtained the information before the patient's visit to the outpatient clinic (time point 0). Three months prior (time point −3) and 3 months after (time point +3) the intervention, pharmacy records were also screened for drug interactions. The number of drug interactions (total and per patient) was determined at the three different time points (−3, 0, +3). In addition, drug interactions encountered at time points −3 and 0 were checked for their presence at time points 0 and +3, respectively, for both intervention arms.**

Results: **Arms A and B included 115 and 105 patients, respectively. Patient characteristics of both intervention arms were similar at time point 0. The number of interactions and the number of patients with interactions were similar in both intervention arms at time point 0. There were 42 and 40 potential drug interactions in 30 and 24 patients in arms A and B, respectively. The reduction in the number of interactions per patient over time and after intervention was small but significant, and was equal in both intervention arms. The advice of the clinical pharmacist had thus no additional value.**

Conclusion: **Both interventions were effective in reducing the number of drug interactions per patient. The advice of a clinical pharmacist was, however, redundant in the studied setting.**

***Keywords*: clinical pharmacist, drug interactions, HIV outpatients, intervention**

INTRODUCTION

Human immunodeficiency virus-1 (HIV-1) infection can nowadays be effectively treated with the use of combination therapy, also described as highly active antiretroviral therapy (HAART). HAART typically consists of a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one or two protease inhibitors (PIs) (1). Although not recommended as first choice in the treatment of HIV-1, the use of triple NRTI regimens can be an alternative (1, 2). HAART has led to a decrease in both morbidity and mortality (3–5) thereby making HIV-1 infection a chronic disease.

A major disadvantage of NNRTIs and PIs is their potential for drug–drug interactions. Both NNRTIs and PIs are extensively metabolized by the cytochrome P450 enzyme system (CYP450) (6, 7). In addition, their ability to inhibit and/or induce different CYP450 enzymes (6–10) and the ability of some PIs to influence the function of the drug

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transporter P-glycoprotein (11–13), can result in a variety of drug interactions with coadministered agents that are metabolized and/or transported through the same pathways.

An earlier study of HIV-1-infected individuals at our institute (14) revealed that 53% of the drugs that were dispensed by community pharmacies were not documented in the outpatient medical record. It involved mainly drugs coadministered with the antiretroviral agents. This lack of awareness of the patient's complete drug regimen could result in unintended combinations leading to adverse effects and/or decreased efficacy of the drugs involved. It is obvious that full knowledge of a patient's drug regimen is of pivotal importance for the identification of drug–drug interactions.

Several studies have shown the significant contribution of pharmacists in improving patient outcomes in hospitalized as well as ambulatory patients. (15–20). In some of these studies the pharmacist pointed out drug-related problems and advised on various aspects including duration of therapy, choice of drug, maximum daily dose, and drug interactions. (17–20). In contrast, Gauthier *et al.* (15) and Hanlon *et al.* (16) undertook a randomized, controlled trial in which a label system indicating drug-nutrient timing and identification of drug-related problems in elderly with polypharmacy, respectively, was compared with the existing pharmacy system. They showed improved outcome in patients randomized to the intervention arm. We are aware of only two uncontrolled intervention studies (21, 22) including HIV-infected patients, in which all types of drug-related interventions were recorded.

In this study, we evaluated the usefulness of intervention in the case of drug interactions of antiretroviral drugs with coadministered agents by a clinical pharmacist in outpatient HIV-treatment.

METHODS

Patients

The Pharmacy Service Point (PSP), located at the hospital pharmacy of the Slotervaart Hospital (Amsterdam, The Netherlands), played a crucial role in this study. In general, the goal of the PSP is to improve the coordination between inpatient and outpatient pharmaceutical care. Its specific service for the HIV-outpatient clinic was to give the treating infectious disease specialist a complete list of drugs used by the patient from pharmacy records (obtained from the community pharmacy) before the their visit of the outpatient clinic.

Patients with a scheduled outpatient visit and who had signed the informed consent to allow access to their community pharmacy records were included in this study. In general, HIV-infected individuals visit the outpatient clinic every 3–4 months. The patients included were consecutive outpatient clinic attendees seen after a fixed date (start date inclusion). Each patient could be included only once in the study.

Study design

A week before the visit of the patient to the outpatient clinic, the patient's pharmacy records, including the dispensed drugs during the last 6 months, were obtained from the community pharmacy by the PSP. Pharmacy records from the community pharmacy, which use computer based systems documenting each drug dispensation per patient, can be considered complete when it concerns recording of drug deliveries (23). From these pharmacy records, the currently used drugs (at the day of visit to the outpatient clinic) were extracted. Subsequently, a trained clinical pharmacist screened the list of drugs for potential drug interactions (24) (see http://www.hiv-druginteractions.org), and, when applicable, an advice linked to a specific drug interaction was formulated.

The study design included two intervention arms (A and B), which were both preceded by an observational (retrospective) control period. Figure 1 displays the study design. In arm A a list with the currently used drugs extracted from pharmacy records was provided to the treating physician. In arm B the same list was provided but with a notification when a drug interaction was present and an advice on how to handle it. The information that was provided on the potential drug interaction consisted of three items: (i) the antiretroviral drug and the coadministered drug involved, (ii) the possible effect of the drug interaction, and (iii) an advice such as: (a) monitor efficacy or toxicity of the implicated drug, (b) dose adjustment, or (c) an alternative therapy. For both intervention arms, the infectious disease specialist obtained the information before the visit of the patient. The date of the scheduled visit

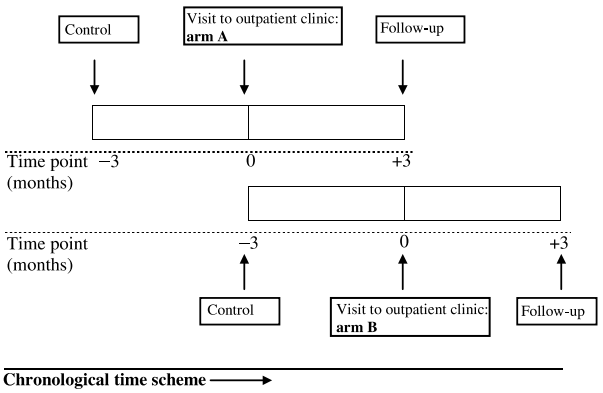

Fig. 1. Sequential study design, in which arm A includes a list of currently used drugs and arm B includes the list with currently used drugs plus identification of drug interactions and an advice linked to the specific drug interaction.

is referred to as time point 0. Duration of inclusion of patients in both arms was until approximately 100 patients were recruited in each arm (A and B).

For all patients, pharmacy records were screened for currently used drugs and potential drug interactions 3 months before time point 0 (control arm: time point −3). In addition, pharmacy records were obtained again from the community pharmacy 3 months after time point 0, and reviewed again (time point +3).

Rationale for study design

A parallel design, in which a control arm and the two intervention arms would run simultaneously, was not possible in this setting, because of recruitment problems. A sequential design was finally chosen, in which patients were first included in arm A (overview of currently used drugs) followed by inclusion in arm B (overview and drug interaction information). This design prevents the infectious disease specialist being alerted by the information on potential drug interactions (arm B) before completion of the arm A study. To prevent bias, the infectious disease specialists involved in this study were not informed beforehand about the goal of this study.

Study outcome

Two analyses were performed. First, the total number of potential drug interactions at the three different time points (−3, 0, and +3) was assessed. Secondly, whether the specific drug interactions encountered at time point 0 for the two arms (A and B) and at time point −3 for the associated control arms were still present at time points +3 and 0, respectively was assessed. In case of change in one of the drugs involved in the interactions encountered at time point 0, the reason for this change was extracted from the outpatient medical record.

Drug interactions

Data regarding drug interactions with antiretroviral drugs are still limited, although new information appears regularly. Therefore, a list of potential drug interactions from the available literature published in journals, as abstracts from congresses, reviews and manufacturers' package inserts, was developed (24). These potential drug interactions were classified by potential severity (25). This classification includes three levels of severity. Grade 1 interactions are those for which the clinical significance is generally not life threatening, although toxicity or loss of efficacy could occur. Grade 2 interactions are potentially serious, but monitoring of plasma concentrations may minimize clinical consequences. Plasma concentrations were, however, not monitored within the scope of this study. Examples include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and antiarrhythmics. Grade 3 interactions are the most serious and may lead to serious and/or life-threatening reactions. Examples include the interaction of PIs with cisapride, terfenadine, astemizole, and midazolam, which can cause cardiac arrhythmias with the former three drugs, and increased or prolonged sedation with the latter drug, respectively. Also included in this category are agents (e.g. rifampin and rifabutin) that dramatically decrease plasma concentrations of the antiretroviral drugs in addition to serious adverse events as a result of increases in their own plasma concentrations.

The number of drug interactions and the degree of severity (grades 1–3) were assessed at time points −3, 0, and +3.

Statistical analysis

Statistical calculations were performed with SPSS for Windows (version 10; SPSS Inc., Chicago, IL,

USA). A *P*-value of 0.05 or less was considered statistically significant. Mann–Whitney *U*-test and Pearson chi-square test were used to compare continuous and categorical patient characteristics, respectively, of arms A and B at time point 0. Bivariate correlation was used to test for relations between patient characteristics. The number of patients with potential drug interactions and the number of potential drug interactions of arm A were compared with those of arm B (Mann–Whitney *U*-test), both at time points −3 (control) and 0. Differences between number of potential drug interactions at time points 0 and +3, and time points −3 and 0 were tested using the Wilcoxon matched-pairs signed-rank test for both arms A and B, and the associated control arms, respectively. Whether the intervention applied in arm B was more effective than applied in arm A in reducing potential drug interactions was tested by using the difference in number of potential drug interactions per patient at time points 0 and +3 as dependent variable (Mann–Whitney *U*-test).

For the comparison of the total number of drug interactions at the different time points, the Kruskal–Wallis test was used.

RESULTS

Patient characteristics and use of antiretroviral drugs

During the first period (arm A), 138 patients were scheduled for a routine visit at the outpatient clinic. Nineteen patients could not be included in the analysis, because of the death of a patient just before the scheduled visit (one), admission to the hospital (one), late or non-receipt of pharmacy records (three), rescheduling of appointment (four), and change of community pharmacy between the time of permission to obtain the pharmacy records and the planned visit or no recently available information on drug use (10). Therefore, 119 patients were included in arm A. Four patients in this arm changed to another community pharmacy after their visit at time point 0, and evaluation at time point +3 was, therefore, not possible. The complete analysis was thus performed with the 115 patients with no missing data on drug use. During the second period (arm B), 130 patients were scheduled for a routine visit, but 106 patients were included in arm B. The reasons for exclusion were hospital admission (one), late or non-receipt of pharmacy records (three), rescheduling of appointment (nine), and change of community pharmacy between the time of permission to obtain the pharmacy records and the planned visit or no recently available information on drug use (11). One patient changed to another community pharmacy between the visit at time point 0 and the time point at which a follow-up evaluation was performed (time point +3), thus leaving 105 patients in arm B.

Table 1 shows the patient characteristics at time point 0. Arms A and B were comparable with parameters listed in Table 1. Overall, one patient was taking amprenavir (0·5%), 12 were taking indinavir (6·1%), 11 were taking nelfinavir (5·6%), three were taking lopinavir (1·5%), 19 were taking ritonavir (9·6%), and 11 were taking saquinavir (5·6%). Nevirapine and efavirenz were administered to 134 (67·7%) and seven (3·5%) patients, respectively.

Overall, patients with relatively low CD4 cell counts and high plasma $\log_{10}$ HIV-RNA were using significantly more drugs (antiretroviral plus coadministered drugs) ($r = -0{\cdot}22$, $P = 0{\cdot}001$, and $r = 0{\cdot}18$, $P = 0{\cdot}008$, respectively) (Fig. 2), and no correlation was observed between the number of antiretroviral drugs (range: 0–6, no patients with monotherapy) and the number of CD4 cell counts and the plasma $\log_{10}$ HIV-RNA.

Total number of drug interactions at time points −3, 0, and +3

The total number of potential drug interactions with the severity rating for both arms at time points −3, 0, and +3 are shown in Table 2. The total number of potential drug interactions increased from 36 to 42 and to 48 in 115 patients at time points −3, 0, and +3, respectively, in arm A. For arm B, the total number of potential drug interactions increased from 33 to 40 and to 43 in 105 patients at time points −3, 0, and +3, respectively. The increase in total number of potential drug interactions in arms A and B was not significant ($P > 0{\cdot}05$ for both comparisons).

Detailed analysis of drug interactions at time point −3, 0, and +3

The number and the severity rating of potential drug interactions for both arms at time point 0 are

Table 1. Baseline patient characteristics (time point 0)

	Total (n = 220)		Arm A[a] (n = 115)		Arm B[b] (n = 105)		
Parameter	Value	IQR	Value	IQR	Value	IQR	P*
Median age (years)	42·6	38·1–50·3	42·6	37·1–49·6	42·6	39·0–50·9	0·29
Male/female (%)	193/27 (87·7/12·3)		100/15 (87·0/13·0)		93/12 (88·6/11·4)		0·72
Median CD4 cell count (cells/μL)	425	300–628	410	310–590	460	280–690	0·47
Median plasma $\log_{10}$ HIV-1 RNA (copies/mL)	<2·30	<2·30–3·23	<2·30	<2·30–3·26	<2·30	<2·30–3·13	0·22
Median number of drugs	4·5	3·0–6·0	5·0	3·0–6·0	4·0	3·0–7·0	0·84
Median number of antiretroviral drugs	3·0	3·0–3·0	3·0	3·0–3·0	3·0	3·0–3·0	0·53
Use of HAART including PI or NNRTI (%)	175 (79·5)		97 (84·3)		78 (74·3)		0·07
Use of PI/no PI (%)	38/182 (17·3/82·7)		20/95 (17·4/82·6)		18/87 (17·1/82·9)		0·96
Use of two PIs/no two PIs (%)	18/202 (8·2/91·8)		9/106 (7·8/91·2)		9/96 (8·6/91·4)		0·84
Use of NNRTI/no NNRTI (%)	145/75 (65·9/34·1)		79/36 (68·7/31·3)		66/39 (62·9/37·1)		0·36
Use of PI + NNRTI/no PI + NNRTI (%)	8/212 (3·6/96·4)		2/113 (1·7/98·3)		6/99 (5·7/94·3)		0·07
Use of two PIs + NNRTI/no two PIs + NNRTI (%)	5/215 (2·3/97·7)		1/114 (0·09/99·1)		4/101 (3·8/96·2)		0·14

[a]Arm in which only a list of currently used drugs was available.

[b]Arm in which a list of currently used drugs was available plus an advice on possible drug interactions.

*P-value when arm A was compared with arm B: Mann–Whitney U-test, Pearson chi-square test.

IQR, interquartile range; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

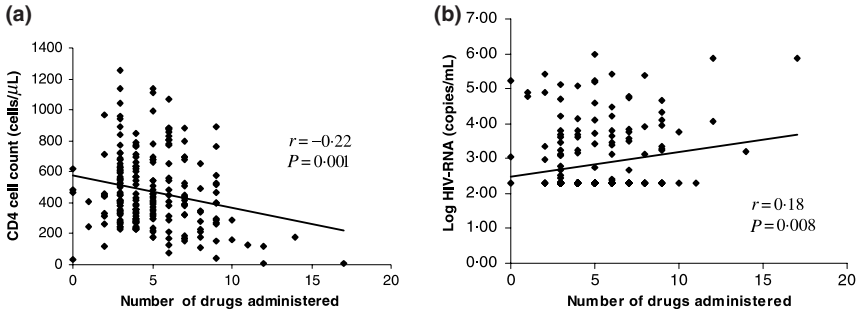

Fig. 2. CD4 cell count (a) and $\log_{10}$ HIV RNA (b) vs. number of drugs administered systemically. Solid line in both figures represents the regression line.

Table 2. Total number of potential drug interactions at the three different time points

	Time point −3		Time point 0		Time point +3		
	Interactions	Mean per patient	Interactions	Mean per patient	Interactions	Mean per patient	*P*-value
Arm A (n = 115)							
Total	36	0·31	42	0·37	48	0·42	
Grade 1	25	0·22	29	0·25	27	0·23	
Grade 2	6	0·05	8	0·07	13	0·11	
Grade 3	5	0·04	5	0·04	8	0·07	
Difference (%)[a]			+16·7				0·72*
Difference (%)[b]					+14·3		
Arm B (n = 105)							
Total	33	0·31	40	0·38	43	0·41	
Grade 1	25	0·24	28	0·27	33	0·31	
Grade 2	8	0·08	12	0·11	10	0·10	
Grade 3	0	0	0	0	0	0	
Difference (%)[a]			+21·2				0·84*
Difference (%)[b]					+7·5		

[a]Difference between time point 0 and −3.
[b]Difference between time point +3 and 0.
*Difference in total number of drug interactions of arms A and B at time point −3, 0 and +3.

presented in Table 3. There were 42 and 40 potential drug interactions in 30 and 24 patients in arms A and B, respectively. Only two potential drug interactions were pharmacodynamic in nature, the remaining were of pharmacokinetic in nature. The most common potential drug interactions at time point 0 were with benzodiazepines (n = 17, 20·7%), methadone (n = 12, 14·6%), and SSRIs (n = 9, 11%). Of the antiretroviral drugs, the most common potential drug interactions were with nevirapine (n = 48, 58·5%), ritonavir (n = 7, 8·5%), and stavudine (n = 6, 7·3%). Of all observed potential pharmacokinetic drug interactions (n = 80), 51, 5, and 24 would probably result in an effect on the exposure of the coadministered drug, on both drugs, or on the antiretroviral drug, respectively. Three patients from arm A had five grade 3 interactions. These involved diazepam and indinavir, a combination of ritonavir and saquinavir with simvastatin, and dual PI therapy including ritonavir and saquinavir with midazolam.

The number of patients with interactions was similar in the different arms both at time point −3 (Table 3, column in the section 'Control period')

Table 3. Reduction in potential drug interactions during the intervention periods and the associated control periods

	Control period				Intervention period			
	Time point −3		Time point 0		Time point 0		Time point +3	
	Interactions	Patients with interactions[a]	Interactions	Patients with interactions[a]	Interactions	Patients with interactions[a]	Interactions	Patients with interactions[a]
Arm A (n = 115)								
Total	36	26	31	24	42	30	30	22
Severity rating								
Grade 1	25 (69·4)	21 (80·8)	21 (67·7)	19 (79·2)	29 (69)	24 (80)	16 (53·3)	17 (77·3)
Grade 2	6 (16·7)	6 (23·1)	5 (16·1)	4 (16·7)	8 (19)	8 (26·7)	6 (20)	5 (22·7)
Grade 3	5 (13·9)	3 (11·5)	5 (16·1)	3 (12·5)	5 (11·9)	3 (10)	5 (16·7)	3 (13·6)
Arm B (n = 105)								
Total	33	21	28	17	40	24	32	19
Severity rating								
Grade 1	25 (75·8)	16 (76·2)	22 (78·6)	14 (82·4)	28 (70)	19 (79·2)	23 (71·9)	16 (84·2)
Grade 2	8 (24·2)	7 (33·3)	6 (21·4)	5 (29·4)	12 (30)	7 (29·2)	9 (28·1)	4 (21·1)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a]Notice that the data reflect that some patients have more than one interaction and interactions with different grades.

and 0 (Table 3, column in the section 'Intervention period') ($P = 0{\cdot}64$ and 0·58, respectively). In addition, the number of potential interactions at time point −3 (Table 3, column in the section 'Control period') and 0 (Table 3, column in the section 'Intervention period') in both arms was similar ($P = 0{\cdot}65$ and 0·57, respectively).

Both arms A and B showed a small but significant, decrease in the number of interactions per patient when time point 0 was compared with time point +3 (1·40 to 1·00 interactions per patient; $P = 0{\cdot}004$ and 1·67 to 1·33 interactions per patient; $P = 0{\cdot}011$, respectively; Table 3, columns in the section 'Intervention period'). The effect of the intervention was similar in the two arms ($P = 0{\cdot}61$). The associated control periods of arms A and B did not result in a significant decrease in the number of interactions per patient when time point −3 was compared with time point 0 ($P = 0{\cdot}06$ for both control periods; Table 3, columns in the section 'Control period').

In arm A, 11 combinations of interacting drugs were changed at time point +3 of which 10 had one of the implicated drugs discontinued and one had an appropriate dose adjustment of the implicated drug. Three drugs were only used in a short course, and all other drugs involved in the potential drug interactions were discontinued for unknown reasons. Of the eight combinations of interacting drugs in arm B that were changed at time point +3, two had an appropriate dose adjustment of the implicated drug, and six had the drug discontinued. Reasons for drug discontinuation were adverse events (not caused by the potential drug interaction) (2), but one of the implicated drugs in the other four interactions was discontinued for unknown reasons.

DISCUSSION

The aim of this study was to investigate whether it was useful for a clinical pharmacist to evaluate drug use and drug interactions in ambulatory HIV-infected patients. The availability of information on drug use with or without the extra service of an alert for drug interaction reduced the number of potential drug interactions per patient significantly (Table 3). However, no difference was observed between arms A and B. These results indicate that, although both interventions were effective, the advice of a clinical pharmacist had no additional value.

Patients with low CD4 cell counts and high plasma $\log_{10}$ HIV-RNA used more drugs (Fig. 2). Patients with immune system depletion (and thus low CD4 cell counts) are more susceptible to opportunistic infections, and if CD4 cell counts decrease to <200 cells/μL, prophylaxis is recommended (26). In addition, with the deterioration of the immune system, susceptibility to bacterial, fungal, viral, and parasitic organisms increases, resulting in for example dermatologic and gastrointestinal complications that also need pharmacotherapy (27). Coadministered drugs commonly used by HIV-infected patients are often metabolized via the CYP450 system (like rifampicin, itraconazole, clarithromycin, and statins) thereby increasing the risk for drug interactions with the administered antiretroviral drugs. Preston *et al.* (25) have shown that patients with the highest risk of having a drug interaction including a PI were those maintained on more drugs. In addition, in this study the number of drug interactions per patient increased when an increased number of drugs were administered (data not shown).

A quarter of our studied patients (54/220) was receiving at least one drug that had a potential drug interaction with one of the antiretroviral drugs used at time point 0. Although the frequency of grade 3 drug interactions was low, the overall potential for a drug interaction, and thus toxicity or loss of efficacy, was relatively high. Most drug interactions, which included nevirapine would most likely result in decreased levels of the coadministered agent due to moderate induction of CYP450 enzymes by nevirapine (28) rather than an effect on nevirapine's activity.

The design of the study does not identify the cause of a change in drug regimen, as this was not documented. However, the fact that both arms A and B showed significant reductions in potential drug interactions compared with the control arm clearly demonstrated the effect of the intervention. Furthermore, we used the outpatient medical record to document the possible reasons for changes, but this source was not detailed enough for this purpose. In addition, general practitioners and other specialists could also have prescribed coadministered drugs and thus reduction of all observed potential drug interactions by this intervention would have been unrealistic. Moreover, a coadministered agent could have been initiated

(and the dosage titrated) much earlier with good tolerability and efficacy.

In a retrospective study performed by Preston *et al.* (25), nearly half of the patients initiating a PI-containing regimen were receiving at least one drug known to cause a potential drug interaction. The incidence of drug interactions in our study is overall lower [0·37 (82/220) vs. 0·67 (111/165), respectively]. Additionally, Preston *et al.* observed that 29 of the 165 patients had a severity I interaction (equal to grade 3 in this study) at baseline vs. three of the 220 patients in our study. Although, the setting of the study by Preston and colleagues was also a HIV specialty clinic, the collaboration of many years' standing between the Department of Internal Medicine and the Department of Pharmacy and Pharmacology at our hospital may have contributed to the higher awareness of potential severe drug interactions. Worth noting is also the intervention performed by the community pharmacy, where drug dispensing is closely monitored for potential drug–drug interactions.

In conclusion, by providing a complete overview of drug use by HIV-1-infected patients the number of potential drug interactions per patient reduced. The advice of a clinical pharmacist did not improve on the positive effect, probably because the infectious disease specialists concerned were sufficiently aware of any drug interactions when they saw the complete overview of the medications used by their patients. Although the effect on clinical outcome in this population is not known, it is obvious that drug–drug interactions in HIV-treatment must remain a subject of attention and that it is pivotal that medical doctors have easy access to a complete medication overview for each of their patients.

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