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Pharmacotherapy of Hospitalised HIV-Infected Patients in a General Hospital during 1990, 1997 and 2001

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Abstract

Objective: To describe the changes over time in drug therapy (antiretroviral as well as co-administered drugs) in HIV-infected patients who required hospitalisation during the period 1990–2001. In addition, we wanted to evaluate and compare the characteristics of these patients.

Design/setting: Retrospective review of hospitalisations of HIV-infected patients in a general hospital.

Results: During specified periods in 1990, 1997 and 2001, 22 patients out of 130 outpatients, 29 out of 394 outpatients, and 19 out of 570 outpatients, respectively, who were treated at the outpatient clinic were admitted 30, 38 and 27 times, respectively. The mean duration of these hospitalisations was 18.8, 14.2 and 16.7 days, respectively. The percentage of women and the mean age of the hospitalised patients increased over the studied time period. AIDS-related diagnoses decreased when comparing 1997 with 2001. The type of co-administered drugs of patients who required hospitalisation was fairly stable, but the total volume (defined as the mean volume of drugs per patient per bed-day) increased dramatically from 5.3 in 1990 to 6.8 in 1997 and to 15.5 in 2001. Dual and triple antiretroviral therapy decreased and became quadruple or greater therapy when 1997 and 2001 were compared. In addition, the number of hospitalised patients not treated with antiretroviral drugs increased from 1997 to 2001.

Conclusion: The incidence of hospital admissions decreased but the volume of co-administered drugs increased from 1990 to 2001, suggesting extensive co-morbidity in the patients who still require hospitalisation.

Since 1987, the year in which the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine was licensed, a large number of new antiretroviral drugs have become available. With the increase in the class of NRTIs, and the introduction of two new classes since 1996, i.e. the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs), combination therapy became the cornerstone of treatment in HIV-1 infection. This combination therapy, now described as highly active antiretroviral therapy (HAART), has resulted in a striking decrease in morbidity and mortality.[1-4] Several studies have demonstrated the shift in healthcare resource use from inpatient to outpatient services, which could be explained by the introduction of HAART.[5-7] Although the use of HAART has been proven effective, patients still have health problems that need to be dealt with. Opportunistic infections, malignancies, drug dependence, psychiatric disorders or hepatic disease and many other complications may occur and may require hospitalisation.

In this study, we wanted to describe the changes over time in the composition of drug therapy (antiretroviral as well as co-administered drugs) during hospitalisation during specified periods in 1990, 1997 and 2001. In addition, we wanted to evaluate and compare the characteristics of these HIV-infected patients.

Methods

The Slotervaart Hospital in Amsterdam, The Netherlands, is a general hospital with approximately 400 beds. The outpatient clinic of the department of Internal Medicine of the Slotervaart Hospital has a central function (among some other hospitals) in the Netherlands with regard to the treatment and healthcare of HIV-infected individuals.

In this study, all HIV-infected patients who were admitted to the hospital (excluding day-ward visits and visits to the outpatient clinic) during the period October through December 1997 and during the period January through July 2001 were included. Hospital admissions of all patients to the Slotervaart Hospital are electronically recorded and coded. HIV-infected patients can be identified by specific codes, which were the same during each time period. The following information was collected during each hospital admission: age, sex, date of admission, date of discharge, and reason(s) for admission. In addition, medical records, nursing records and pharmacy records were used to extract data concerning drugs prescribed during admission. Drugs prescribed during admission could have been introduced at the hospital (both short- and long-term treatment) or be a continuation of therapy that was already in use before admission. For both antiretroviral drugs and co-administered drugs, specific information was gathered: prescribed daily dose (PDD), frequency of administration, route of administration, and duration of use. As a similar study was performed in this hospital from January through September 1990,[8] changes in pharmacotherapy for the patient population could be compared between the three time periods.

Drug Utilisation

The defined daily dose (DDD) is the average recommended daily dose for the main indication of the drug. The prescribed daily dose (PDD) is the total prescribed daily dose of the drug. For each patient admitted to the hospital for several days, the ratio of the PDD and the DDD of a drug was calculated. This ratio was then multiplied by the duration of treatment for each drug resulting in the prescribed volume of a drug per patient.

For some drugs, the DDD was not (yet) available. Thus, for these drugs the usual dosages prescribed in the Netherlands (for the main indication of the drug) were used. Drugs applied locally (skin and mucous membrane) are not associated with a DDD.[9] In addition, in practice it did not appear possible to ascertain the applied amount of these formulations, and these types of drugs are therefore excluded from analysis. Agents used for diagnostic purposes and supplementary nutrition (parenteral or drip-feed) were also excluded from analysis.

Furthermore, all co-administered drugs besides

the antiretroviral regimen were grouped according to the Anatomical Therapeutical and Chemical (ATC) classification codes drawn up by the World Health Organization (WHO).[9] In this classification, each formulation of a drug, thus not each drug, is classified according to its main indication. For each ATC-code group (main anatomical group, i.e. the site at which treatment is directed), the volume of drugs expressed in DDD per 100 bed-days, an accepted technical unit of measurement in drug utilisation studies in hospitals,[10] was also calculated.

Finally, the type of antiretroviral regimen (monotherapy, dual therapy, triple therapy and quadruple therapy or more) that had been prescribed prior to hospital admission was assessed.

Results

Patients

From 1 October to 31 December 1997 and from 1 January to 31 July 2001, 29 and 19 HIV-infected patients, respectively, were admitted to the Internal Medicine Ward of the Slotervaart Hospital (table I). The total number of hospitalisations during these time periods was 38 and 27, respectively. The information collected during the first three-quarters of 1990 is also included in table I. During this time period, 22 HIV-infected patients were admitted to the hospital 30 times, the mean age (37.5 years) was lower than during 1997 and 2001, and all patients except one were men.

Percentage Hospitalised, Type and Duration of Admission

The number of outpatients treated at the outpatient clinic increased during the studied time period from 130 in 1990, to 394 in 1997, and to 570 in 2001. During the first 9 months of 1990, the last quarter of 1997, and the first 7 months of 2001, the percentages of patients admitted to the hospital were 16.9%, 7.4%, and 3.3%, respectively. For comparison, percentages of patients admitted to the hospital calculated over 1 year were 22.6%, 29.4% and 5.7% for 1990, 1997 and 2001, respectively (table I).

The mean number of inpatient days of all admissions fluctuated during the studied time period from 18.8 days in 1990 to 14.2 days in 1997 and to 16.7 days in 2001 (table I).

Patients were admitted to the hospital for a variety of reasons (table II). In 1997, most diagnoses associated with hospital admissions were AIDS-related, such as Kaposi's sarcoma (KS), lymphoma, ocular infections caused by cytomegalovirus (CMV), and toxoplasmosis. Diagnoses classified as 'other' included for example reflux oesophagitis, sinusitis, arthritis and renal failure. In 2001, with the exception of the diagnoses *Mycobacterium avium* complex (MAC) [one patient admitted three times], dementia (one patient), and recurrent pneumonias (one patient admitted twice), other diagnoses were not typically AIDS-related, although one patient had a primary HIV and CMV infection. Abscess of the vulva, an allergic reaction, otitis externa, and

Table I. Description of the study populations

	January–September 1990	October–December 1997	January–July 2001
Total no. of outpatients	130	394	570
No. of patients hospitalised	22	29	19
Mean age in years (range)	37.5 (24–53)	42.0 (28.6–64.8)	42.2 (30.7–57.4)
Male/female ratio (%)	21/1 (95.5/4.5)	25/4 (86.2/13.8)	15/4 (78.9/21.1)
Total no. of hospitalisations	30	38	27
Mean no. of inpatient days (range)	18.8 (2–75)	14.2 (2–80)	16.7 (2–67)
Total inpatient days	564	527	450
Percentage of patients hospitalised (calculated over 1 year)	16.9 (22.6)	7.4 (29.4)	3.3 (5.7)

Table II. Reasons for hospital admission

Diagnosis	No. of hospitalisations[a]	
	Oct–Dec 1997 (n = 38)	Jan–Jul 2001 (n = 27)
Haematological abnormalities	3	1
Kaposi's sarcoma	3	
Lung infections	7[b]	7[c]
Gastrointestinal events	8	5
Lymphoma	4	
Ocular infections[d]	2	
Pancreatitis	3	
Toxoplasmosis	2	
Mycobacterium avium		3
General 'malaise'		2
Liver/gallbladder problems		6
Dementia		1
Primary HIV/CMV infection		1
Other	8	6
AIDS-related diagnoses (%)	16 (40)	6 (18.8)
Total diagnoses	**40**	**32**

a Patient may have been admitted because of more than one condition.
b Of which two were *Pneumocystis carinii* pneumonia and three were tuberculosis.
c Of which one was *Pneumocystis carinii* pneumonia.
d Of which one was cytomegalovirus and one was herpes zoster ophthalmica.
CMV = cytomegalovirus.

poorly regulated diabetes mellitus were examples of diagnoses classified as 'other' in 2001.

Pharmacotherapy

Drugs co-administered during hospital admissions presented as the number of hospitalisations during which they were prescribed, are listed in table III. Information for one patient, who was admitted to the hospital during the first semester of 2001 because of gastrointestinal problems, was missing, and this patient was thus excluded from further analysis. When comparing the three time periods, it appeared that this list has largely not changed over time. Cotrimoxazole, folic acid, paracetamol and temazepam were all present in the top 10 co-administered drugs in each of the time periods. In addition, two drugs have been replaced by other analogues, but have the same application: heparin and ketoconazole (1990) were replaced by nadroparin calcium and fluconazole, respectively (1997 and 2001). Furthermore, the Slotervaart Hospital pharmacy changed the gastric proton pump inhibitor in its formulary from omeprazole to pantoprazole between 1997 and 2001.

When all the co-administered drugs were taken into account, the total volume of drugs per patient per bed-day has increased from 5.3 in 1990 to 6.8 in 1997 and 15.5 in 2001. This is illustrated in figure 1, in which the volume of drugs is presented as the DDD per 100 bed-days for the different ATC-code groups. The increase in prescribed volume is not associated with one ATC-code group

Table III. Top ten co-administered drugs used during hospital admissions presented as the number of admissions in which the co-administered drug is prescribed

Drugs in 1990	30 hospitalisations (% drug prescribed)	Drugs in 1997	38 hospitalisations (% drug prescribed)	Drugs in 2001	26[a] hospitalisations (% drug prescribed)
Folic acid	22 (73)	Cotrimoxazole	19 (50)	Cotrimoxazole	17 (65)
Cotrimoxazole	20 (67)	Omeprazole	15 (39)	Paracetamol	14 (54)
Ketoconazole	15 (50)	Fluconazole	12 (32)	Fluconazole	13 (50)
Heparin	14 (47)	Nadroparin calcium	12 (32)	Ciprofloxacin	11 (42)
Paracetamol	13 (43)	Folic acid	11 (29)	Temazepam	11 (42)
Nystatin	12 (40)	Paracetamol	10 (26)	Nadroparin calcium	10 (38)
Pentamidine	9 (30)	Clindamycin	8 (21)	Potassium chloride	9 (35)
Aciclovir	9 (30)	Domperidone	8 (21)	Furosemide	8 (31)
Lactulose	9 (30)	Lactulose	8 (21)	Folic acid	7 (27)
Temazepam	8 (27)	Temazepam	8 (21)	Pantoprazole	7 (27)

a Information for one patient, who was admitted to the hospital during the first semester of 2001 because of gastrointestinal problems, was missing, and this patient was thus excluded from further analysis.

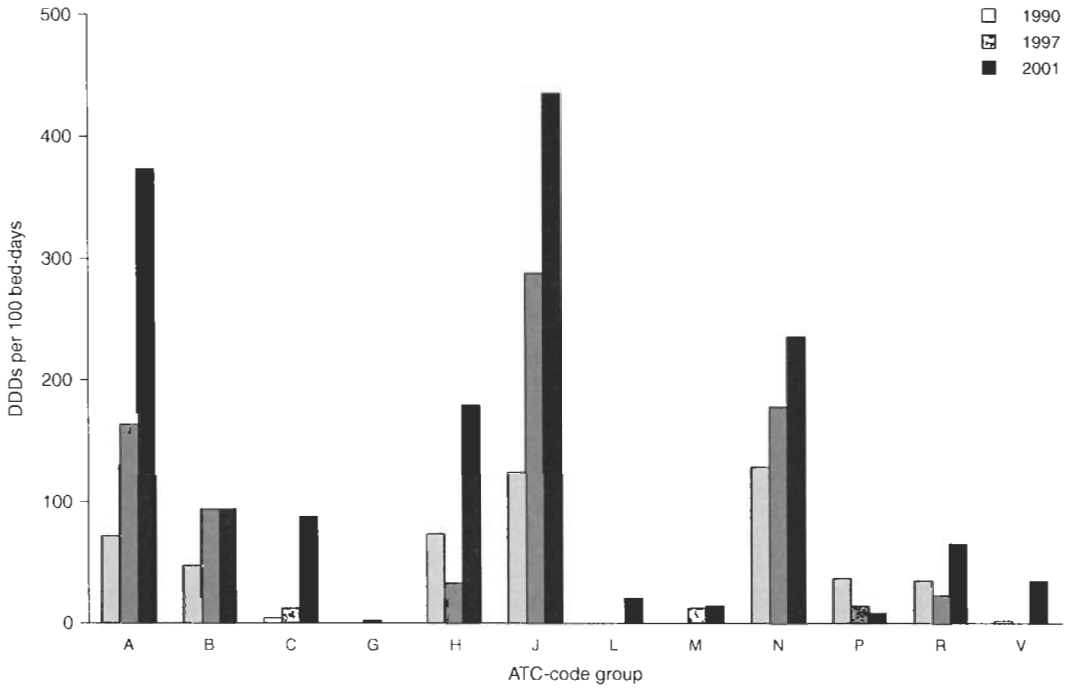

Fig. 1. The defined daily dose (DDD) per 100 bed-days for co-administered drugs presented in groups according to Anatomical Therapeutical and Chemical (ATC) classification codes drawn up by the World Health Organization (WHO)[9] for 1990, 1997 and 2001.
A = gastrointestinal tract and metabolism; **B** = blood and blood-forming organs; **C** = cardiovascular agents; **G** = urogenital tract and sex hormones; **H** = systemic hormonal preparations; **J** = systemic antimicrobial agents; **L** = oncolytics and immune modulators; **M** = musculoskeletal agents; **N** = central nervous system drugs; **P** = antiprotozoals; **R** = respiratory tract drugs; **V** = antidotes, treatment of alcoholism.

as almost each group shows an increase in prescribed volume. Exceptions are ATC-code group P (antiprotozoals), H (systemic hormonal preparations) and R (respiratory tract), the latter two of which show a dip in 1997, after which an increase was again seen in 2001 compared with both 1990 and 1997. The largest increases are seen with ATC-code group A (gastrointestinal tract and metabolism), C (cardiovascular agents), H (systemic hormonal preparations), and J (systemic antimicrobial agents). The introduction of drugs from ATC-code group L (oncolytics and immune modulators) in 2001 is notable, consisting of filgrastim and hydroxycarbamide. In the treatment of HIV infection, hydroxycarbamide is formally used as an antiretroviral agent (to potentiate the efficacy of didanosine in particular); however, it is classified here as a co-administered agent.

Table IV presents the drugs used most during hospital admission, including the antiretroviral drugs, when comparing the volume of drugs prescribed (PDD/DDD × duration of hospitalisation in days). For each time period, some new drugs (besides the antiretroviral drugs) appeared in the list when compared with table III, most likely because of the usage of high dosages of these drugs (like dexamethasone, methadone and prednisolone) in some patients. The appearance of the co-formulation of lopinavir and ritonavir in this list is notable as it only became available via

Table IV. Top ten medications used during hospital admissions (antiretroviral drugs in bold type)

Drugs in 1990	PDD/DDD × duration of hospitalisation (days) [no. (%)]	Drugs in 1997	PDD/DDD × duration [no. (%)]	Drugs in 2001	PDD/DDD × duration [no. (%)]
Dexamethasone	429 (13.9)	Fluconazole	579 (13.2)	Prednisolone	561 (7.2)
Lactulose	297 (9.6)	Methadone	322 (7.3)	Lactulose	559 (7.1)
Ketoconazole	274 (8.9)	Omeprazole	303 (6.9)	Itraconazole	454 (5.8)
Haloperidol	244 (7.9)	Nadroparin calcium	273 (6.2)	**Lamivudine**	261 (3.3)
Folic acid	239 (7.8)	**Lamivudine**	270 (6.1)	Nadroparin calcium	248 (3.2)
Pyrimethamine	199 (6.5)	**Stavudine**	212 (4.8)	**Lopinavir/ritonavir**	206 (2.6)
Phenytoin	162 (5.3)	**Saquinavir**	152 (3.5)	Temazepam	192 (2.5)
Nystatin	126 (4.1)	Lactulose	137 (3.1)	Amoxicillin/clavulanic acid	191 (2.4)
Zidovudine	117 (3.8)	Clindamycin	125 (2.8)	Ciprofloxacin	189 (2.4)
Paracetamol	97 (3.1)	Prednisolone	112 (2.6)	Potassium chloride	184 (2.3)
Total	**2184 (70.8)**		**2485 (56.6)**		**3045 (38.9)**
Total all drugs	**3083 (100)**		**4392 (100)**		**7834 (100)**

DDD = defined daily dose (the average recommended daily dose for the main indication of the drug); **PDD** = the total prescribed daily dose of the drug.

Table V. Antiretroviral drugs administered during hospitalisation

Antiretroviral drug	No. of hospitalisations in 1997 (total = 38)	PDD/DDD × duration of hospitalisation (days)	PDD/DDD per day	No. of hospitalisations in 2001 (total = 26)[a]	PDD/DDD × duration of hospitalisation (days)	PDD/DDD per day
NRTIs						
Abacavir				5	93	1.0
Didanosine	1	4	1.0	2	29	1.0
Lamivudine	25	270	1.0	12	261	1.0
Stavudine	21	212	1.0	7	98	1.0
Zidovudine	8	33	0.4	2	81	1.0
NNRTIs						
Efavirenz				2	12	1.0
Nevirapine	1	9	1.0	6	118	0.8
PIs						
Indinavir	3	27	1.1	2	7	0.6
Lopinavir/ritonavir				10	206	1.2
Nelfinavir				1	5	1.0
Ritonavir	6	36	0.9	2	3	0.4
Saquinavir	8	76	0.8			

a Information for one patient, who was admitted to the hospital during the first semester of 2001 because of gastrointestinal problems, was missing, and this patient was thus excluded from further analysis.

DDD = defined daily dose (the average recommended daily dose for the main indication of the drug); **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **PDD** = the total prescribed daily dose of the drug; **PI** = protease inhibitor.

compassionate use programmes in the Slotervaart Hospital from June 2000. When compared with 1990, antiretroviral therapy has gained an important place in the treatment of HIV-infected individuals during the time periods 1997 and 2001 (table IV). Antiretroviral drugs that were prescribed most during the 1997 time period were lamivudine, stavudine and saquinavir, while this shifted to lopinavir/ritonavir and nevirapine with preservation of the nucleoside backbone of

lamivudine plus stavudine, and the increased use of abacavir in 2001 (table V). Usage deviating from the defined daily dose (DDD) of an antiretroviral drug stands out in a PDD/DDD per day smaller or higher than 1.0. In 1997 zidovudine was prescribed in doses well below the DDD and the same holds true in 2001 for ritonavir and indinavir.

Figure 2 presents the distribution of type of antiretroviral regimen at presentation to the clinic. The figure clearly shows that in 2001 the use of dual and triple therapy decreased and moved to quadruple therapy or more, which includes the use of dual protease inhibitors with ritonavir in a low dose as a pharmacological booster.[11] Also, the number of patients who were not treated with antiretroviral drugs increased from 1997 to 2001.

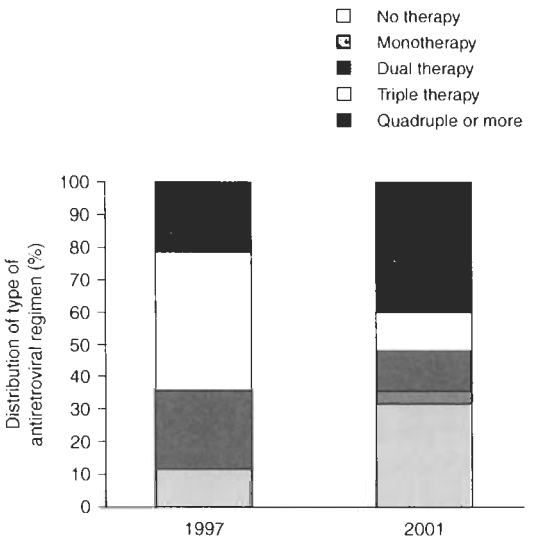

Fig. 2. Types of antiretroviral drug regimens on hospital admission in 1997 and 2001.

Discussion

In this study, we compared the pharmacotherapy and demographic and clinical characteristics of hospital admissions of HIV-infected individuals during the time period 1990–2001. Over time, hospital admissions were characterised by an increased percentage of women and a slight increase in the age of the patients (table I). This trend is a reflection of the growing proportion of new cases of AIDS and HIV infection among women[12] plus the introduction of HAART, which has resulted in increased life expectancy for HIV-infected patients.[1-4] The percentage of patients hospitalised (during 1 year) increased from 22.6% in 1990 to 29.4% in 1997, and thereafter decreased to 5.7% in 2001. The dramatic drop in the percentage of patients hospitalised in 2001 (i.e. 5.7% during 1 year) suggests that, although HAART was introduced in 1996, its advantages were only evident some time later. The trend in duration of admission over time (mean of 18.8, 14.2 and 16.7 days in 1990, 1997 and 2001, respectively) does not parallel the trend observed with the total patient population that is admitted to the Internal Medicine ward at the Slotervaart Hospital; the mean duration of admission in 1990, 1997 and 2001 was 17.9, 10.5 and 10.7 days, respectively. Apparently, HIV-infected patients need a longer time to recover from their complications than non-HIV-infected patients.

The spectrum of diagnoses of hospital admissions has changed when comparing 1997 and 2001 (table II). The number of AIDS-related diagnoses decreased in 2001 compared with 1997, which is probably a direct effect of the introduction of PIs and combination therapy in 1996. In contrast, Mocroft et al.[13] demonstrated that the decline in AIDS-defining illnesses began as early as 1991 and that the incidence of admissions for non-AIDS causes already exceeded that of AIDS-defining illnesses in 1997. They explain this trend through the benefit of dual combination therapy.[13] Another explanation for the low number of AIDS-related diagnoses is the location of the Slotervaart Hospital. This hospital is situated in Amsterdam-West, a part of the city that has a low incidence of patients presenting with opportunistic infections as the first sign of HIV infection, in contrast to the hospitals in the centre of Amsterdam. However, the Slotervaart Hospital does have a high number

of outpatient referrals for HIV treatment from outside the direct area.

The treatment and prophylaxis of opportunistic infections is still an important part of drug therapy (table III). Cotrimoxazole was the most frequently administered drug during hospital admissions in 1997 and in 2001, and the second most frequently administered drug in 1990 (table III). In addition, the frequent use (and in the case of itraconazole, the high dose) of antifungal agents in 1990, 1997 and in 2001 also suggests this (table III and table IV). The extended use of prophylaxis could be a reflection of the type of HIV-infected patients who still require hospital admissions. Primary as well as secondary prophylaxis can safely be discontinued after CD4 cell counts increase in response to HAART.[14] Thus, these patients probably do not have a reasonably immune-competent system in spite of HAART, which was used by most patients (figure 2). The appearance of lopinavir/ritonavir in table IV is consistent with this. Lopinavir/ritonavir was at first (during the first part of 2001) mostly administered as salvage therapy. Thus, the fact that the hospital admissions concern late-stage patients substantiates this observation. Indeed, the mean numbers of CD4 cell counts (range) at presentation to the clinic in 1997 and 2001 were 160 (10–420) and 133 (5–520) cells/μL, respectively, of which 64.7 and 73.1% were less than 200 cells/μL.

The types of co-administered drugs for patients that require hospitalisation have not changed much, but the volume has increased dramatically. This also confirms the above-mentioned statement that patients who require hospitalisation are probably patients with end-stage AIDS (and thus low CD4 cell counts) and/or patients with extensive co-morbidity. Increases in the use of co-medication from ATC-code groups A, H and J are mostly a result of the extensive use of lactulose, prednisolone and itraconazole, respectively (figure 1). Lactulose is used for constipation resulting from prolonged inactivity during hospital admission. Drugs from ATC-code groups J and H are administered to treat divergent infections. The increased use of drugs to treat infections in 2001 may again be a reflection of the condition of the patients who were admitted to the hospital. The increase in use of drugs from ATC-code group C may be a consequence of the fact that HIV is more and more becoming a chronic disease. The result is that the treatment of co-existing morbidity is receiving equal priority as these patients live much longer. However, it is probably fortuitous that among the HIV-infected patients who were admitted in 2001, cardiovascular co-morbidity was present.

Figure 2 shows that in 2001 monotherapy for HIV was still in use. The reason for administration of monotherapy in this patient was to prevent AIDS dementia as she refused further treatment with HAART. The increased number of patients who were not treated with antiretroviral drugs could reflect the expectative attitude of the infectious disease specialist towards initiating aggressive treatment in patients with a normal number of CD4 cells. In addition, in patients who are admitted to hospital in a very bad condition, antiretroviral treatment is often temporarily discontinued, and patients admitted with opportunistic infection and recently diagnosed HIV infection are treated first for their opportunistic infection.

The deviation in the normal dosage of some antiretroviral drugs can easily be explained (table V). Nevirapine is administered according to an escalating dosage regimen when first starting the drug (i.e. 200mg once daily for the first 2 weeks). A number of patients admitted to the hospital started nevirapine treatment in the hospital. PIs are often used in a combined regimen with ritonavir, both in a decreased dosage, which explains the PDD/DDD per day of PIs being lower than 1.0 in both 1997 and 2001. Although the registered dosage of lopinavir/ritonavir is 400/100mg (three capsules) twice daily, a dosage of 533/133mg (four capsules) twice daily is administered when combined with NNRTIs, resulting in an increased PDD/DDD per day. The reason for a deviating value for zidovudine in 1997 (0.4) results from the DDD of 1500mg that was registered in 1997 when the drug was first marketed. Sub-

sequently, a daily dose of 600mg appeared to be as effective, but resulted in less adverse events, and therefore became the usual dosage. The deviations in values for the PIs and NNRTIs suggest the application of tailor-made antiretroviral therapy.

Conclusions

Over time, hospital admissions were characterised by an increased percentage of women and an increase in the age of the patients. The percentage of patients admitted to the hospital (over 1 year) has decreased dramatically over recent years, and probably involves patients in very poor health. Consistent with this, the volume of co-administered drugs has increased, suggesting extensive co-morbidity in these patients.

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