DOI: 10.1111/hiv.12441

HIV Medicine (2016)

ORIGINAL RESEARCH

Ageing with HIV: do comorbidities and polymedication drive treatment optimization?*

L Cuzin,[1,2,3] C Katlama,[4,5] L Cotte,[6,7] P Pugliese,[8] A Cheret,[9,10,11] C Bernaud,[12] D Rey,[13] I Poizot-Martin,[14,15] C Chirouze,[16,17] F Bani-Sadr[18,19] and A Cabié[20,21] for the Dat'AIDS Study Group†

[1]INSERM, UMR 1027, Toulouse, France, [2]Toulouse III University, Toulouse, France, [3]COREVIH, CHU Toulouse, Toulouse, France, [4]UPMC Univ Paris 06, UMR_S 1136, Pierre Louis Institute of Epidemiology and Public Health, Sorbonne Univ, Paris, France, [5]Infectious Diseases Department, Pitié Salpêtrière, AP-HP, Paris, France, [6]Infectious Diseases Department, Hospices Civils de Lyon, Lyon, France, [7]INSERM U1052, Lyon, France, [8]Infectious Diseases Department, CHU Archet, Nice, France, [9]EA 3620, Université Paris-Descartes, Sorbonne Paris Cité, Paris, France, [10]Infectious Diseases Department, Tourcoing General Hospital, Tourcoing, France, [11]Internal Medicine Unit, Bicêtre Hospital, AP-HP, Paris, France, [12]Infectious Diseases Department, CHU Hotel Dieu, Nantes, France, [13]Le Trait d'Union, HIV care Center, CHU Strasbourg, Strasbourg, France, [14]Immuno-Hematology Clinic, APHM Hôpital Sainte-Marguerite, Aix-Marseille Univ, Marseille, France, [15]Inserm U912 (SESSTIM), Marseille, France, [16]UMR CNRS 6249 Chrono-Environnement, Franche-Comté University, Besançon, France, [17]Infectious Diseases Department, Besançon University Hospital, Besançon, France, [18]EA-4684/SFR CAP-SANTE, Reims Champagne-Ardenne University, Reims, France, [19]Tropical and Infectious Diseases, Hôpital Robert Debré, CHU Reims, Reims, France, [20]Infectious Diseases Department, Université Antilles, Guyane, EA 4537 and [21]Franch West Indies University, Fort de France, France

Objectives

The aim of the study was to describe the ageing HIV-infected population (> 50 years old) and their current antiretroviral therapy (ART), comorbidities and coprescriptions in France in 2013 and to compare them to the younger population.

Methods

A retrospective analysis of a prospectively collected database was performed. The characteristics of patients receiving ART as well as their current ART and their numbers of comorbidities and comedications at the censoring date (1 July 2013) were compared between patients ageing with HIV infection, patients who seroconverted while ageing, and younger patients.

Results

We compared 10 318 ageing patients [median age 56 years; 25% interquartile range (IQR) 53–62 years] with 13 302 younger patients (median age 42 years; 25% IQR 36–47 years). The ageing patients were more frequently male than the younger patients (77 *vs.* 65%). Among the ageing patients, 7025 were diagnosed with HIV infection before 2000 and represented a distinct group, the 'experienced ageing' group, by comparison with the 'recently diagnosed ageing' group. Triple therapy containing a boosted protease inhibitor was used in 28.2% of the patients (*vs.* 39% and 36% of the younger and "recently diagnosed ageing" groups, respectively); a nonnucleoside reverse transcriptase inhibitor in 27% (*vs.* 33% and 38%, respectively), an integrase strand transfer inhibitor (INSTI) in 9% (*vs.* 7% and 9%, respectively), and another regimen (fewer or more than three drugs) in 35.8% (*vs.* 21% and 16.5%, respectively). "Experienced ageing" patients typically had one or more comorbidities (62.1%) and were receiving at least one comedication (71%). Central nervous system (CNS) agents (prescribed in 44.6% of the "experienced ageing" patients) and antilipidaemics (in 44.2%) were the most frequently prescribed comedications. INSTIs were used in 23% of the population and were used

Correspondence: Dr Lise Cuzin, COREVIH, Hopital Purpan, TSA40031, 31059 Toulouse, Cedex 9, France. Tel: (+33) 561779043; e-mail: cuzin.l@chu-toulouse.fr

*This work was presented in part as a poster at the 15th European AIDS Conference, Barcelona, Spain, 21—4 October 2015.

†See Appendix.

significantly more often in patients with comorbidities and coprescriptions. For all comparisons, $P < 0.0001$.

Conclusions

In ageing HIV-infected patients, especially those with a long history of HIV infection, comorbidities and coprescriptions are highly prevalent.

Keywords: ageing with HIV, comorbidity, drug–drug interactions, polypharmacy

Accepted 14 July 2016

Introduction

Since potent antiretroviral therapy (ART) became available, HIV-related mortality has been steadily decreasing in high-income countries [1]. Compared with the general population, the relative risk of death is no longer elevated in French HIV-infected individuals successfully treated with ART [2]. As a direct consequence, the HIV-infected population in care is ageing. In France, the percentage of HIV-infected patients 50 years of age or older increased from 8.5 to 42% for men and from 6 to 27% for women between 2003 and 2012 [2]. Moreover, this ageing population is diverse, including patients diagnosed while ageing and patients diagnosed many years ago and ageing with HIV infection [3].

A North American study found that multi-morbidity was present in 65% of HIV-infected patients [4], and, as in the general population, multiple chronic conditions accumulated with increasing age [5]. Because of this comorbidity, a wide variety of drugs (e.g. antidepressants or statins) are prescribed along with antiretroviral drugs. However, the combination of these drugs produces a high potential for drug–drug interactions (DDIs) that may result in either loss of efficacy or increased toxicity of the respective drugs. In a recent Spanish study, 292 potential DDIs were found in 268 patients, mainly involving boosted protease inhibitors (bPIs), benzodiazepines, nonsteroidal anti-inflammatory drugs, nonnucleoside reverse transcriptase inhibitors (NNRTIs), corticosteroids, proton pump inhibitors and antithrombotics [6]. In the same study, it was found that clinically significant interactions were strongly related to the use of ritonavir-boosted PIs because of the mixed inducer/inhibitor effects of ritonavir on different cytochrome P450 pathways [7]. Thus, an important issue in the future will be the optimal management of multi-morbidity and multidrug exposure [8]. Integrase strand transfer inhibitors (INSTIs), a new well-tolerated ART class with metabolic properties driving few DDIs [9,10], at least for those who do not need a pharmacological booster, have recently become available and their use may be beneficial in the ageing population to avoid DDIs.

Using a large prospective French database, we described the ageing population, the prevalence of various comorbidities and the prescription of comedications, and the choice of ART regimens.

Methods

Information was collected from 11 large HIV reference centres in France. These hospitals maintain prospective databases of all HIV-1-infected patients who seek care in the centres and provide written consent. The data collection has been approved by the French National Commission on Informatics and Liberty (CNIL). The databases are implemented via an electronic medical record (EMR) [11]. The patients enter the databases when they seek care in one of the centres, regardless of their HIV disease history, and all previous clinical events as well as therapeutic history are collected with the appropriate dates. The EMR collects demographic details, clinical events, antiretroviral history, viral load and CD4 T-cell count data for patients at regular 3- to 6-month intervals during routine clinical assessment. This system allows the use of the databases with minimal delay, limited to automatic and manual quality controls required before any analysis.

For the purposes of this study, we selected all patients on ART who presented to at least one medical visit between 1 January 2009 and 1 July 2013 (the censoring date). The collected demographic characteristics were sex, the most probable route of HIV acquisition, and CD4 T-cell count and viral load value before starting ART. Age, body mass index (BMI), the presence of hepatitis C virus (HCV) coinfection, Centers for Disease Control and Prevention (CDC) class, total ART duration and current regimen were collected at the censoring date. In the case of HCV coinfection, history of HCV treatment was also collected. Unfortunately, the databases do not collect socioeconomic characteristics such as social isolation, employment status, education level or receipt of financial welfare. The medical history was searched to collect data on past or current diabetes, hypertension, dyslipidaemia, cardiovascular diseases, neurovascular diseases, depression, cancer, and sexual dysfunction. Renal insufficiency

was defined by an estimated glomerular filtration rate <60 ml/min/1.73 m², as calculated using the Modification of Diet in Renal Disease (MDRD) formula. The patients' medical prescriptions were searched for concomitant use of medications with potential DDIs when used with ART. We retained the following drug classes, using the Anatomical Therapeutic Chemical classification [12]: nonsteroidal anti-inflammatories (NSAIs), corticosteroids, vitamin K antagonists, tuberculosis treatments, cardiovascular drugs, cancer chemotherapy, fibrates, statins, post-transplant immunosuppressive agents, proton pump inhibitors, psychiatric medications (including hypnotics), and erectile dysfunction treatments.

Patients were classified as "ageing" if they were > 50 years old at the censoring date. To distinguish those recently diagnosed from those with long-term ART experience, the "recently diagnosed ageing" group was composed of ageing patients with an HIV diagnosis made after 2000, in contrast to ageing patients diagnosed before 2000, who were defined as "experienced ageing" patients. Their characteristics, comorbidities and coprescriptions were compared with those of patients who were ≤ 50 years old. Because INSTIs that do not require cobicistat or ritonavir pharmacological boosters are responsible for fewer DDIs than other ART classes [13], we also analysed the proportions of patients who received an INSTI across diverse comorbidities and comedications. As a consequence of the study period used, raltegravir was the only INSTI that we could consider. Continuous variables were described by their medians and 25% interquartile ranges (IQRs) and compared between groups using a Mann–Whitney test. Categorical variables were described by proportions and compared using chi-squared tests.

Results

Among 23683 HIV-infected patients fulfilling the inclusion criteria, 10318 were > 50 years old and represent the ageing group (median age 56 years; 25% IQR 53–62 years), and 13302 were ≤ 50 years old and represent the younger group (median age 42 years; 25% IQR 36–47 years). Among the ageing group, 7025 patients were diagnosed with HIV infection before 2000 and constituted the "experienced ageing" population. The characteristics of the overall population and the comparisons between the groups are summarized in Table 1. Ageing patients were more frequently male than younger patients: 77% of the ageing group *vs*. 65% of the younger group were male. Notably, the "experienced ageing" patients had been treated for twice as long as the "recently diagnosed ageing" and younger populations. On the censoring date,

Table 1 Patients' characteristics, and comparisons between the younger patients, recently diagnosed ageing patients, diagnosed after 2000 ('recent'), and experienced ageing patients, with a long HIV history ('exp.')

	Total (n = 23683)	≤50 years old (n = 13302)	Ageing, recent (n = 3293)	Ageing, exp. (n = 7025)	P*
Sex (% men)	70.5	65.2	76.7	77.7	<0.0001
Hepatitis C virus coinfection (%)	12.4	9.8	6.3	20.3	<0.0001
Most probable route of HIV acquisition (%)					
Men who have sex with men	39.8	40.4	32.9	42.1	<0.0001
Heterosexual	41.4	43.4	53.8	31.7	
Injecting drug use	9.1	6.7	2.2	16.7	
Other	9.7	9.5	11.1	9.5	
CDC class C (%)	24.2	20	26.6	31.2	<0.0001
Body mass index (kg/m²) (%)					
<18.5	10.3	10.8	7.7	10.5	<0.0001
18.5–24	57.1	57.9	48.5	59.9	
25–30	24.1	22.8	31.3	23.0	
>30	8.6	8.6	12.5	6.7	
Duration of known infection (years) [median (25% IQR)]	14 (7–21)	11 (6–18)	8 (5–11)	22 (18–26)	<0.0001
Duration of ART (years) [median (25% IQR)]	11 (5–16)	8 (4–14)	7 (4–10)	16 (14–19)	<0.0001
Pre-ART CD4 count (cells/mL) [median (25% IQR)]	280 (158–402)	298 (180–424)	237 (97–346)	269 (151–390)	<0.0001
Pre-ART viral load (log copies/ml) [median (25% IQR)]	4.7 (4.1–5.3)	4.7 (4.1–5.2)	4.9 (4.4–5.5)	4.7 (3.8–5.3)	<0.0001
Number of different ART regimens [median (25% IQR)]	4 (2–7)	3 (2–6)	3 (2–4)	7 (4–9)	<0.0001

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range.
*Comparisons between the three patient groups.

28.2% of the "experienced ageing" patients were receiving triple ART based on a bPI (*vs.* 39% and 36.5% of the younger and "recently diagnosed ageing" populations, respectively), 27% were receiving an NNRTI (*vs.* 33% and 38%, respectively), 9% were receiving an INSTI (*vs.* 7% and 9%, respectively), and 35.8% were receiving another regimen (fewer or more than three drugs) (*vs.* 21% and 16.5%, respectively) ($P < 0.0001$).

Among the 2939 patients with HCV infection, 20% of the population were spontaneously cured, with no difference between the age groups. Among the HCV treatment-naïve patients, patients' refusal and medical contra-indication were more frequent in the ageing group than in the younger group (17 *vs.* 9%, respectively; $P < 0.0001$). Among the patients with past HCV treatment (54% of the ageing group *vs.* 49% of the younger group; $P < 0.0001$), no difference between the age groups was found in the treatment results. Overall, 42% of the treated patients had sustained HCV suppression, and 58% were in need of new HCV treatment.

Only 37.9% of the "experienced ageing" population did not have any comorbidity, compared with 67.5% of the younger group and 44.1% of the "recently diagnosed ageing" population. Table 2 shows details of the comorbidities for the total population and the comparisons between groups. Among the patients with at least one comorbidity, ART was based on a bPI in 31.2% of the patients (*vs.* 34.8% of the patients with no comorbidity), on an NNRTI in 29.7% (*vs.* 38.6%, respectively), on an INSTI in 10.3% (*vs.* 6.2%, respectively), and on another regimen in 28.8% (*vs.* 20.4%, respectively) ($P < 0.0001$).

There were statistically significant differences between the groups in the percentage of patients not receiving any comedication: only 29.2% of the "experienced ageing" population, 47.2% of the younger group and 33.4% of the "recently diagnosed ageing" group were not receiving any comedication. Table 3 shows details of comedications for the total population and the comparisons between groups. Among the patients receiving at least one comedication, ART was based on a bPI in 32.8% of the patients (*vs.* 38.5% of the patients with no comedication), on an NNRTI in 30.6% (*vs.* 32.8%, respectively), on an INSTI in 9.3% (*vs.* 5.1%, respectively), and on another regimen in 27.3% (*vs.* 23.5%, respectively) ($P < 0.0001$).

Table 4 shows the proportions of patients who had been treated with INSTI-based ART with regard to the presence of a specific comorbidity or comedication, independent of patient group. The proportion of INSTI-experienced patients increased from 17.1% in the absence of comorbidity to 47.2% in the case of five or more comorbidities. Similarly, the proportions of INSTI-experienced patients increased from 14.3% of patients receiving no comedication to 34.2% of patients receiving five or more drugs along with their ART.

Table 2 Proportion of patients with comorbidities, and comparisons between the younger patients, recently diagnosed ageing patients, diagnosed after 2000 ('recent'), and experienced ageing patients, with a long HIV history ('exp.')

	Total	≤50 years old	Ageing, recent	Ageing, exp.	*P**
Diabetes (%)	5.5	2.6	9.1	9.4	<0.0001
Hypertension (%)	12.6	6.3	22.6	19.4	<0.0001
Renal insufficiency† (%)	5.7	2.6	9.8	9.4	<0.0001
Dyslipidaemia (%)	17.0	10.9	19.8	27.4	<0.0001
Cardiovascular diseases (%)	5.7	2.7	7.4	10.5	<0.0001
Neurovascular diseases (%)	1.5	0.7	3.1	2.3	<0.0001
Depression (%)	16.1	14.2	13.3	20.9	<0.0001
Sexual dysfunction (%)	1.9	1.2	2.3	3.1	<0.0001
Cancer (%)	10.4	6.7	12.5	16.6	<0.0001
Number of comorbidities (%)					
0	55.4	67.5	44.1	37.9	<0.0001
1	25.9	22.8	30.8	29.5	
2	11.2	6.9	15.3	17.3	
3	5.1	2.2	6.1	9.8	
4	1.8	0.4	2.7	3.8	
≥5	0.6	0.2	1.0	1.7	

*Comparisons between the three patient groups.
†Estimated glomerular filtration rate <60 ml/min/1.73 m² as calculated using Modification of Diet in Renal Disease (MDRD).

Discussion

In this large prospective cohort of French patients living with HIV, comorbidity was frequent. In the ageing population with a long HIV history, 62.1% of patients had at least one comorbidity. Dyslipidaemia, hypertension and depression were the most frequent comorbidities. Coprescriptions were similarly frequent, with 71% of the ageing population with a long HIV history receiving at least one drug class concomitant to ART, and as many as 10% of them receiving five or more drug classes. Psychiatric agents (including hypnotics) and cardiovascular drugs were the most commonly coprescribed drug classes.

Protease inhibitor-based ART was less frequently prescribed in ageing patients and in patients with comorbidity and coprescriptions; nevertheless, it was still used in approximately 30% in each group. INSTIs were used more frequently in patients with multiple comorbidities and comedications. Although we cannot draw any inferences from this cross-sectional study, the findings emphasize that this class is often preferd when DDIs are of concern.

Multi-morbidity has been related to mortality [14], poor quality of life and greater risk of drug toxicity [4] and has already been described as increasing in the

Table 3 Proportion of patients with coprescription in addition to antiretroviral therapy (ART), and comparisons between the younger patients, recently diagnosed ageing patients, diagnosed after 2000 ('recent'), and experienced ageing patients, with a long HIV history ('exp.')

	Total	≤50 years old	Ageing, recent	Ageing, exp.	*P**
NSAIs (%)	9.9	9.6	9.7	10.7	0.027
Corticosteroids (%)	3.5	3.2	4.6	3.7	0.001
Vitamin K antagonists (%)	4.1	3.7	4.8	4.6	0.001
Tuberculosis treatments (%)	2.0	2.2	2.9	1.4	<0.0001
Cardiovascular drugs (%)	30.2	22.9	39.3	39.7	<0.0001
Cancer chemotherapy (%)	1.2	1.1	1.2	1.1	0.79
Fibrates (%)	7.1	5.6	7.1	10.1	<0.0001
Statins (%)	25.2	18.8	32.1	34.1	<0.0001
Post-transplant agents (%)	0.9	0.9	0.9	0.9	0.93
Proton pump inhibitors (%)	21.0	18.5	24.1	24.4	<0.0001
Psychiatric medications† (%)	39.5	36.5	40.4	44.6	<0.0001
Erectile dysfunction treatments (%)	3.8	3.0	5.2	4.7	<0.0001
Number of comedications (%)					
0	39.9	47.2	33.4	29.2	<0.0001
1	20.6	20.2	20.5	21.7	
2	14.0	11.8	16.1	17.3	
3	9.6	7.2	11.3	13.4	
4	6.9	5.7	8.1	8.7	
≥5	8.8	7.9	10.6	9.7	

NSAI, nonsteroidal anti-inflammatory.
*Comparisons between the three patient groups.
†Including hypnotics.

ageing HIV-infected population [8]. Some of these comorbidities may be induced or aggravated by ART [15–18]. It is of growing importance for HIV physicians to limit the use of these drugs and to provide counselling for healthy ageing, with particular attention to patients ageing with a long HIV history, as they represent a distinct group from those who have seroconverted while ageing [3].

Polypharmacy is of growing interest in patients ageing with HIV infection [6,7,19–21]. In another prospective European cohort [22], the same proportion of patients receiving comedications was described, highlighting the ongoing potential for serious DDIs in HIV practice as a result of polypharmacy. Actually, in a study specifically designed to look for DDIs, Evans-Jones *et al.* found that 27% of the studied prescriptions could lead to DDIs, with a risk for a potential reduction of ART efficacy in 15% of cases [23]. Ritonavir-boosted PIs were shown to be frequently associated with relevant DDIs in a study in which the authors emphasized that there is a great opportunity for pharmacists to become more involved by applying their knowledge in helping the physician to optimize treatments [6]. Interestingly, the Work Group for the HIV and Aging Consensus Project, among other recommendations, stresses that the primary care provider should perform an annual medication review to limit toxicity and DDIs and that we should recommend that our patients use one pharmacy and, if possible, use an HIV specialty pharmacy [19]. Hence, a multidisciplinary approach to ART management, including physicians, virologists and pharmacists, is recommended in France to prevent the risk of DDIs and to optimize clinical management [24].

INSTIs began being used in 2009 [25], with confirmed good efficacy and tolerance in ART-naïve patients [26]. Furthermore, replacing bPIs with raltegravir has been shown to be virologically noninferior and to improve the patients' lipid profiles [27]. The availability of new drugs in the INSTI class offers an opportunity to reduce drug and pill burdens for our patients, at least when using INSTIs that do not need a pharmacological booster.

We analysed a large, prospective, multicentre cohort of more than 23600 patients in care in France, including overseas territories, enabling us to describe a substantial group of ageing patients. Because of the population size, we were able to distinguish ageing patients with a long HIV history from those who seroconverted while ageing. Nevertheless, our study has some limitations. Some coprescriptions may have been underestimated, as the physician may not feel it necessary to write them on the patient's medical chart. Notably, cancer chemotherapy, which was prescribed by other specialized physicians, was clearly absent from our database. However, this underestimation reinforces our findings. This cross-sectional retrospective analysis of our database did not allow us to assess the multifactorial cause of any ART modification, and thus the growing use of INSTIs with comorbidities and coprescriptions may not be related to the analysed issues. Nevertheless, our results seem to be

Table 4 Proportions of patients who received integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy (ART) (past or current), with regard to the presence of a specific comorbidity or comedication

	INSTI experienced	INSTI naïve	*P**
Overall (%)	23.2	76.8	<0.0001
Comorbidities (%)			
Absence of comorbidity	17.1	82.9	<0.0001
Hepatitis C	29.8	70.1	<0.0001
Diabetes	35.6	64.4	<0.0001
Hypertension	30.4	69.6	<0.0001
Renal insufficiency†	45.5	54.5	<0.0001
Dyslipidaemia	32.4	67.6	<0.0001
Cardiovascular diseases	39.9	60.1	<0.0001
Neurovascular diseases	34.7	65.3	<0.0001
Depression	31.5	68.5	<0.0001
Sexual dysfunction	33.6	66.4	<0.0001
Cancer	36.2	63.8	<0.0001
Coprescriptions (%)			
Absence of coprescription	14.3	85.7	<0.0001
NSAIs	29.3	70.7	<0.0001
Corticosteroids	39.8	60.2	<0.0001
Vitamin K antagonists	34.3	65.7	<0.0001
Tuberculosis treatments	40.0	60.0	<0.0001
Cardiovascular drugs	31.1	38.9	<0.0001
Cancer chemotherapy	31.7	68.3	0.0006
Fibrates	33.4	66.6	<0.0001
Statins	31.7	68.3	<0.0001
Post-transplant immunosuppressive agents	42.0	58.0	<0.0001
Proton pump inhibitors	34.8	65.2	<0.0001
Psychiatric medications‡	29.6	70.4	<0.0001
Erectile dysfunction treatments	31.3	68.7	<0.0001
Number of comorbidities (%)			
0	17.1	82.9	<0.0001
1	26.7	73.3	
2	32.3	67.7	
3	42.2	57.8	
4	42.9	57.1	
≥5	47.2	52.8	
Number of comedications (%)			
0	14.3	85.7	<0.0001
1	23.1	76.9	
2	30.1	69.9	
3	32.1	67.9	
4	33.9	66.1	
≥5	34.2	65.8	
Patient group (%)			
Patients <50 years old	18.9	81.1	<0.0001
Recently diagnosed ageing patients	20.3	79.7	
Experienced ageing patients	32.6	67.4	

NSAI, nonsteroidal anti-inflammatory.
*Comparisons between patients with the comorbidity or coprescription and those without.
†Estimated glomerular filtration rate <60 ml/min/1.73 m² as calculated using Modification of Diet in Renal Disease (MDRD).
‡Including hypnotics.

consistent with some degree of willingness to reduce toxicity and potential DDIs.

In conclusion, we showed that, in a population with very frequent comorbidities and coprescriptions, physicians should be aware of the risks of toxicity and DDIs, with particular attention being paid to ageing patients with a long HIV history.

Acknowledgements

Conflicts of interest: The authors declare no conflicts of interest regarding the study.

Author contributions

Lise Cuzin and AC designed the study. Lise Cuzin performed the analysis and wrote the first version of the article. CK, Laurent Cotte, PP, AC, CB, DR, IP-M, CC and FB-S were responsible for the data collection and quality control in their centre. All authors revised the manuscript and provided advice, and they all agree with the final version.

References

1 Morlat P, Roussillon C, Henard S *et al.* Causes of death among HIV-infected patients in France in 2010 (national survey): trends since 2000. *AIDS* 2014; **28**: 1181–1191.
2 Costagliola D. Demographics of HIV and aging. *Curr Opin HIV AIDS* 2014; **9**: 294–301.
3 Guaraldi G, Zona S, Brothers TD *et al.* Aging with HIV vs. HIV seroconversion at older age: a diverse population with distinct comorbidity profiles. *PLoS ONE* 2015; **10**: e0118531.
4 Kim DJ, Westfall AO, Chamot E *et al.* Multimorbidity patterns in HIV-infected patients: the role of obesity in chronic disease clustering. *J Acquir Immune Defic Syndr* 2012; **61**: 600–605.
5 Kendall CE, Wong J, Taljaard M *et al.* A cross-sectional, population-based study measuring comorbidity among people living with HIV in Ontario. *BMC Public Health* 2014; **14**: 161.
6 Iniesta-Navalon C, Franco-Miguel J, Gascon-Canovas J, Rentero-Redondo L. Identification of potential clinically significant drug interactions in HIV-infected patients: a comprehensive therapeutic approach. *HIV Med* 2015; **16**: 273–279.
7 Burgess MJ, Zeuli JD, Kasten MJ. Management of HIV/AIDS in older patients-drug/drug interactions and adherence to antiretroviral therapy. *HIV/AIDS* 2015;**7**:251–264.
8 Hasse B, Ledergerber B, Furrer H *et al.* Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis* 2011; **53**: 1130–1139.
9 Correll T, Klibanov OM. Integrase inhibitors: a new treatment option for patients with human immunodeficiency virus infection. *Pharmacotherapy* 2008; **28**: 90–101.
10 Osterholzer DA, Goldman M. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. *Clin Infect Dis* 2014; **59**: 265–271.

11 Pugliese P, Cuzin L, Cabie A *et al*. A large French prospective cohort of HIV-infected patients: the Nadis Cohort. *HIV Med* 2009; **10**: 504–511.
12 WHO Collaborating Center for Drug Statistics Methodology. ATC/DDD Index 2015. Available at http://www.whocc.no/atc_ddd_index/ (accessed 21 August 2015).
13 Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clin Infect Dis* 2009; **48**: 931–939.
14 Hentzien M, Dramé M, Allavena C *et al*. Impact of age-related comorbidities on five-year overall mortality among elderly HIV-infected patients in the late HAART era–role of chronic renal disease. *J Nutr Health Aging* 2015; **00**: 1–7.
15 Flandre P, Pugliese P, Cuzin L *et al*. Risk factors of chronic kidney disease in HIV-infected patients. *Clin J Am Soc Nephrol* 2011; **6**: 1700–1707.
16 Reyskens KM, Fisher TL, Schisler JC *et al*. Cardio-metabolic effectsof HIV protease inhibitors (lopinavir/ritonavir). *PLoS ONE* 2013; **8**: e73347.
17 Sension M, Deckx H. Lipid metabolism and lipodystrophy in HIV-1-infected patients: the role played by nonnucleoside reverse transcriptase inhibitors. *AIDS Rev* 2015; **17**: 21–36.
18 Apostolova N, Funes HA, Blas-Garcia A, Galindo MJ, Alvarez A, Esplugues JV. Efavirenz and the CNS: what we already know and questions that need to be answered. *J Antimicrob Chemother* 2015; **70**: 2693–2708.
19 Work Group for the HIV and Aging Consensus Project. Summary report from the human immunodeficiency virus and aging Consensus Project: treatment strategies for clinicians managing older individuals with the human immunodeficiency virus. *J Am Geriatr Soc* 2012; **60**: 974–979.
20 Krentz HB, Gill MJ. The impact of non-antiretroviral polypharmacy on the continuity of antiretroviral therapy (ART) among HIV patients. *AIDS Patient Care and STDs* 2015; **30**: 11–17.
21 Marzolini C, Elzi L, Gibbons S *et al*. Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010; **15**: 413–423.
22 Acquah R, Graham H, Winter A. Quantifying polypharmacy in a large HIV-infected cohort. *HIV Med* 2015; **16**: 583–584.
23 Evans-Jones JG, Cottle LE, Back DJ *et al*. Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis* 2010; **50**: 1419–1421.
24 Ministère des Affaires sociales de la santé et des droits de femmes. Prise en charge médicale des personnes vivant avec le VIH 2014. Available at http://www.sante.gouv.fr/prise-en-charge-medicale-des-personnes-vivant-avec-le-vih-actualisation-2014-du-rapport-2013.html (accessed 16 October 2015).
25 Lennox JL, DeJesus E, Lazzarin A *et al*. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet* 2009; **374**: 796–806.
26 Lennox JL, Landovitz RJ, Ribaudo HJ *et al*. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized. Controlled Equivalence Trial. *Ann Intern Med* 2014; **161**: 461–471.
27 Martinez E, Larrousse M, Llibre JM *et al*. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS* 2010; **24**: 1697–1707.

Appendix : The Dat'AIDS Study Group

S. Brégigeon, O. Zaegel-Faucher, V. Obry-Roguet, M. Orticoni, M. J. Soavi, I. Luquet-Besson, E. Ressiot, M. Carta- Padovani, M. J. Ducassou, H. Bertone, S. Galie, A Galinier, M. Monclar, P. Martinet, A. S. Ritleng, A. Ivanova, C. Blanco-Betancourt, C. Lions and I. Poizot-Martin (Marseille); B. Marchou, P. Massip, M. Obadia, M. Alvarez, L. Porte, L. Cuzin, P. Delobel, G. Martin-Blondel, A. Debard, M. Chauveau, D. Garipuy, M. Mularczyk, J. Bernard, E. Labau, I. Lepain, M. Marcel, E. Puntis and K. Sauné (Toulouse); P. Pugliese, C. Ceppi, E. Cua, J. Cottalorda, P. Dellamonica, E. Demonchy, B. Dunais, J. Durant, C. Etienne, S. Ferrando, J. G. Fuzibet, R. Garraffo, K. Risso, V. Mondain, A. Naqvi, N. Oran, I. Perbost, S. Pillet, B. Prouvost-Keller, C. Pradier, S. Wehrlen-Pugliese, E. Rosenthal, S. Sausse, P. M. Roger (Nice); C. Allavena, C. Bernaud, E. Billaud, C. Biron, B. Bonnet, S. Bouchez, D. Boutoille, C. Brunet-Cartier, N. Hall, T. Jovelin, P. Morineau, F. Raffi, V. Reliquet, H. Hue, L. Larmet, S. Pineau, V. Ferré, E. André-Garnier, A. Rodallec, F. Vivrel, M. Lefebvre, O. Grossi, C. Biron, P. Point and O. Aubry (Nantes); A. Cheret and P. Choisy (Tourcoing); Y. Yazdanpanah, R. Landman, C. Duvivier, M. A. Valantin, R. Agher, C. Katlama, O. Lortholary, V. Avettand-Fenoel, C. Rouzioux, P. H. Consigny, G. Cessot, F. Touam, R. Usubillaga and K. Benhadj (Paris); A. Cabié, S. Abel, S. Pierre-François, M. Ouka and J. Martial (Fort de France); D. Rey, E. Ebel, P. Fischer, M. Partisani, C. Cheneau, M. Priester, M. L. Batard, C. Bernard-Henry and E. de Mautort (Strasbourg); C. Chirouze, C. Drobacheff-Thiébaut, J. P. Faller, J. F. Faucher, A. Foltzer, H. Gil and L. Hustache-Mathieu (Besançon); B. Hoen (Pointe à Pitre); C. Jacomet, H. Laurichesse, O. Lesens, M. Vidal, N. Mrozek, C. Aumeran, O. Baud, J. Beytout, D. Coban and S. Casanova (Clermont-Ferrand); F. Bani-Sadr, C. Rouger, J. L. Berger, Y. N'Guyen, D. Lambert, I. Kmiec and M. Hentzien (Reims); D. Peyramond, C. Chidiac, F. Ader, F. Biron, A. Boibieux, L. Cotte, T. Ferry, P. Miailhes, T. Perpoint and S. Degroodt (Lyon).