Risk Factors Associated with Older Age in Treatment-Naive HIV-Positive Patients

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Key Words

HIV-1 • HIV transmission • Immune reconstitution • HIV late presenter

Abstract

Background: Older HIV patients are defined as aged 50 years and older. This group is a growing population in developed countries. In order to improve care for older HIV patients, we intended to gain insight into the specific features of transmission, epidemiology, immunology and antiretroviral treatment (ART) of this population. **Patients and Methods:** All patients from the RESINA cohort were analyzed, comprising 2,085 individuals at the beginning of 2010. RESINA is an ongoing study analyzing epidemiological and immunological data, resistance patterns and therapeutic data in treatment-naive HIV-positive patients from North Rhine-Westphalia, Germany. Patients are included in the RESINA cohort at the time of the intended start of ART. For statistical evaluation, we used χ^2 and Mann-Whitney U tests. **Results:** A total of 14.6% of patients in our cohort was above 50 years. Men were significantly more prevalent among older patients (86.8 vs. 78.6%; $p < 0.001$). The proportion of older patients was significantly higher in the heterosexual group (30%) as compared to bisexual (20%), homosexual (13%) and intrave-

nous drug user (4%) modes of transmission ($p < 0.001$). When comparing ethnic groups, older patients were most often found among Caucasians (17 vs. 4% in other groups, $p < 0.001$). No significant difference for transmitted drug resistance patterns was found. The proportion of older patients with CDC stage A was significantly lower than with stages B or C (10 vs. 21 vs. 21%, $p < 0.001$). In older patients, changes of ART regimes were more frequent ($p = 0.015$) and the median CD4 cell count at the start of treatment was lower (176 vs. 200/ μ l, $p = 0.017$). After 72 weeks of ART, the relative increase of CD4 cells was significantly lower in older as compared to younger patients (200 vs. 231/ μ l, $p = 0.017$). **Conclusions:** Our results provide insight into the epidemiology of HIV in the elderly. In our cohort, the typical older patient was a Caucasian male who had acquired HIV through heterosexual contact. The prognosis in older patients is worsened as a result of several unfavorable circumstances, such as delayed start of ART, more frequent treatment changes and diminished immune reconstitution. As a consequence, better strategies for more frequent HIV testing in patients at risk for HIV are needed, and ART should be offered to older patients at earlier time points and higher CD4 cell counts.

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Introduction

Older patients are generally defined as being above 50 years. By the efficacy of antiretroviral treatment (ART), life expectancy in HIV-infected patients continues to increase, and as a consequence, older patients are the fastest growing group of people with HIV in developed countries. In addition to HIV-infected patients getting older, the number of newly diagnosed patients is increasing in the older age group. In Great Britain, for example, the number of older HIV-positive persons seeking care rose 3.5-fold between the years 2000 and 2007 [32]. In Italy, the percentage of older patients living with HIV rose from 5.3 to 10.2% over a period of 11 years, between 1990 and 2001 [34]. In the Swiss HIV Cohort, the number of patients above 50 years old has steadily increased over the past 20 years (www.shcs.ch, accessed November 2010). In Germany, at present every 4th patient living with HIV is above 50 years old [15]. A report from the US Centers for Disease Control and Prevention from 2003 indicates that the cumulative number of AIDS cases in US citizens over 50 quintupled during the previous decade [22] and it can be foreseen that by the year 2015 every 2nd person with HIV in the United States will be above 50 years of age [17].

This changing epidemiology poses new challenges for physicians caring for patients with HIV. Special needs for older patients living with HIV have received little attention in the past and have only recently been acknowledged. Research tailored for older people with HIV has been initiated in several countries. In the UK, the '50 Plus' Survey investigates the needs and concerns of older adults. It shows that older people with HIV are disadvantaged in a wide range of ways – from poorer health to social care and housing problems and significant financial disadvantages compared to their peers (www.tht.org.uk). A comprehensive array of issues, including health status, stigma, depression, social networks, spirituality, sexual behavior and substance abuse, is being analyzed in the ROAH study in New York City (Research on Older Adults with HIV; <http://www.acria.org/research/roah-study>).

In order to provide optimal care for elderly HIV patients, it is important to gain insight into the specific features of transmission, epidemiology, immunology and treatment of this group. The incidence of AIDS-defining illness has steadily decreased over the past decade, while non-AIDS-defining and malignant diseases play an increasing role. In addition, older HIV patients are prone to a variety of age-associated medical comorbidities, for example high blood pressure, altered lipid profiles, diabetes and depression. The management of these age-specific

diseases will play an increasing role and the focus of care will have to expand beyond the improvement of HIV-associated conditions.

So far, studies of responses to ART among older patients mainly involved small populations and limited follow-up [14, 23, 28, 36]. The aim of the present study was to describe epidemiological trends in a large cohort in older patients in Germany and to provide insight into the specific features of transmission, immunology and ART.

Patients and Methods

RESINA is a large prospective and well-characterized cohort of HIV-infected patients in North Rhine-Westphalia, Germany [24]. A total of 35 centers contribute by providing patient data for the cohort, which comprised 2,085 patients at the beginning of 2010. Data from the entire cohort were used in the present analysis. Patients are included in the RESINA cohort at the time of the intended start of ART. Since 2001, RESINA is an ongoing study analyzing epidemiological and immunological data, HIV resistance patterns and therapeutic data in treatment-naïve HIV-positive patients – as also described by Oette et al. [25].

For statistical evaluation, the χ^2 test was used for parametric values and the Mann-Whitney U test was used for nonparametric values. Elderly people were defined as those aged 50 and older at the time of inclusion into the study.

In the RESINA cohort we analyzed unique features of older patients and age-specific risk factors prior to treatment and during ART. Clinical and epidemiological parameters included age, gender, mode of transmission, ethnicity and CDC stage.

Results

Baseline Characteristics

A total of 2,085 patients were analyzed, with a median age of 42 years (range 19–86): 1,781 were younger than 50 years (median 39 years) and 304 patients were 50 years and older (median 56 years). The proportion of older patients in our cohort was 14.6%, and with regard to the year of study inclusion this proportion remained stable, ranging between 12 and 19% (table 1). The proportion of men was significantly higher at older age (78.6 vs. 86.8%, $p < 0.001$). Regular medical care for patients >50 years was more often provided by hospitals as compared to private practices ($p < 0.001$). The proportion of elderly was significantly higher in the heterosexual group (27%), as compared to the groups of homosexual transmission (12.5%), intravenous drug user transmission (3.9%) or HIV transmission in an endemic country (3.2%) ($p < 0.001$, as shown in table 1). When comparing ethnic groups in our cohort, elderly patients were most often

Table 1. Overview over major parameters analyzed

Parameter	Subgroups	Total number	Age <50 n	Median (range)	Age ≥50 n	% of total	Median (range)	Test χ^2	Level of significance
Gender	total	2,085	1,781		304	14.6			0.001
	male	1,664	1,400		264	15.9			
	female	421	381		40	9.5			
Viral load prior to treatment		1,178	1,004		174			MWU	0.418
Viral load week 12		1,018	861	54 (0–240,000)	157		64 (0–20,236)	MWU	0.080
Viral load week 48		861	714	50 (0–1,530,520)	147		50 (0–88,498)	MWU	0.517
CD4 count abs prior to treatment		1,208	1,029	200 (0–1,170)	179		176 (1–851)	MWU	0.017
CD4 increase abs week 12		927	782	108 (–410 to 707)	145		96 (–224 to 655)	MWU	0.171
CD4 increase abs week 48		869	723	378 (0–1,369)	146		332 (36–1,162)	MWU	0.015
CD4 increase abs week 72		853	714	231 (–665 to 1,616)	139		200 (–71 to 900)	MWU	0.017
CD4 increase abs week 108		664	550	266 (–245 to 1,308)	114		233 (–296 to 938)	MWU	0.053
No. of ART regimen (1 vs. 2 vs. ≥3)	total	1,273	1,084		189			χ^2	0.015
	1	675	593		82	12.2			
	2	275	224		51	18.6			
	≥3	323	267		56	17.3			
Duration first-line treatment, days		661	543	179 (5–2,833)	118		167 (5–1,766)	MWU	0.623
Days until 2nd resistance test		382	321	117 (0–2,807)	61		124 (0–2,094)	MWU	0.469
CDC stage	total	796	667		129			χ^2	<0.0001
	A	330	297		33	10.0			
	B	204	162		42	20.6			
	C	262	208		54	20.6			
HIV subtype	total	1,953	1,660		293			χ^2	0.044
	A	231	187		44	19.1			
	B	1,492	1,266		226	15.2			
	C	71	62		9	12.7			
	other	159	145		14	8.8			
Ethnicity	total	2,057	1,757		300			χ^2	<0.0001
	Asian	68	63		5	7.4			
	Afro	270	262		8	3.0			
	Caucasian	1,692	1,406		286	16.9			
	Hispanic	27	26		1	3.7			
Mode of transmission	total	1,920	1,663		257			χ^2	<0.0001
	IVDU	155	149		6	3.9			
	MSM	1,072	938		134	12.5			
	heterosexual	379	277		102	26.9			
	endemic country	285	276		9	3.2			
	other	29	23		6				
HIV caregiver	total	2,066	1,764		302			χ^2	0.001
	clinic	1,474	1,235		239				
	medical office	592	529		63				
Year of inclusion	total	2,085	1,781		304			χ^2	0.794
	2001	92	81		11	12			
	2002	105	90		15	14			
	2003	137	115		22	16			
	2004	238	205		33	14			
	2005	230	187		43	19			
	2006	272	231		41	15			
	2007	377	325		52	14			
	2008	401	345		56	14			
	2009	233	202		31				
HIV primary drug resistance	total	236	196		40			χ^2	0.92
	NRTI	120	95		25				
	NNRTI	59	52		7				
	PI	57	49		8				

MWU = Mann-Whitney U; abs = absolute; MSM = men having sex with men; NRTI = nucleoside reverse transcriptase inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitors.

Fig. 1. Distribution of CDC stages according to patient age younger and older than 50.

Fig. 2. Distribution of drug resistance patterns according to patient age. NRTI = Nucleoside reverse transcriptase inhibitors; NNRTI = nonnucleoside reverse transcriptase inhibitors.

found among Caucasians (16.9 vs. 3.8% in other groups, $p < 0.001$).

Immunological and Virological Parameters

The median CD4 cell count at the start of treatment was lower in the elderly patients (176 vs. 200/ μl , $p = 0.017$). In the long run (after 72 weeks of ART), the relative increase of CD4 cells was significantly higher in younger patients (231 vs. 200/ μl , $p = 0.017$). When comparing CDC stages at the time of first ART, the proportion of elderly patients with stage A was significantly lower than in stages B or C (10 vs. 21 vs. 21%, $p < 0.001$, as shown in fig. 1).

No significant difference between younger and older patients was noted in the viral load prior to ART ($p = 0.418$), in the median viral load under ART at week 48 ($p = 0.517$), or in the amount of transmitted primary resistance ($p = 0.092$).

Response to Treatment

Tolerance and response to first-line ART were comparable in both age groups, as reflected by the median time until change of treatment (117 vs. 124 days). However, the proportion of elderly patients among those with treatment changes was higher than among those with ongoing first-line treatment (17.9 vs. 12.2%, $p = 0.015$).

Drug Resistance

Primary drug resistance was found in 196/1,781 patients (11%) <50 years of age and in 40/304 patients (13%)

aged 50 years and older ($p = 0.92$, χ^2). The frequency of drug resistance at the start of treatment is shown in figure 2. Although not statistically significant, a higher rate of nucleoside reverse transcriptase inhibitor resistance among older patients was noted.

Discussion

The number of older persons living with HIV/AIDS has been increasing in recent years. This increase can be mainly attributed to the success of ART, significantly prolonging life of many HIV-infected persons. On the other hand, older patients have a low awareness of the necessity to protect themselves against sexually transmitted diseases, resulting in an increasing number of newly acquired infections at older age. In a national survey American citizens were analyzed for their frequency of HIV testing. Patients over the age of 50 who are at risk for HIV infection were one fifth as likely to get tested for HIV and one sixth as likely to use condoms compared to at-risk people in their 20s [33]. Doctors more frequently asked questions about HIV risk factors if patients were under 30 as compared to patients above 50 years [29]. In a retrospective analysis, el-Sadr and Gettler [11] found a prevalence of 5% of undiagnosed HIV infections in patients aged 60 years and older. Thus, routine HIV testing is still uncommon in older patients and as a consequence, they have delayed access to HIV care [1, 6, 8, 30]. In order to

improve strategies for prevention and earlier recognition of HIV infection in older patients, recognition of this patient group being at greatest risk is important. In the present study we analyzed age-related differences in a large number of treatment-naïve patients.

Baseline Characteristics

The proportion of men significantly increased with older age (78.6 vs. 86.8%, $p < 0.001$). A similar trend of an increasing male predominance in older age at diagnosis was recently found in the UK (58 vs. 74%) [32].

When comparing ethnic groups in our cohort, elderly patients were most often found among Caucasians (16.9 vs. 3.8% in other groups, $p < 0.001$). In analogy to our findings, in a study by Smith et al. [32] a higher proportion of older heterosexuals were of white ethnicity (42 vs. 16%) when compared with younger heterosexuals.

With regard to the mode of transmission in our cohort, the proportion of older patients was significantly higher in the heterosexual group, as compared to patients who acquired HIV through the other modes of transmission. In analogy to our findings other investigators also found a predominance of heterosexuals among the HIV transmission categories in the older group and among long-term survivors [12, 26]. Other analyses had found sex between men to be the predominant mode of transmission in older patients [32].

Taken together, the above data reveal subgroups of older patients at increased risk for HIV infection and these subgroups differ from younger patients at greatest risk of acquiring HIV. Prevention strategies and educational campaigns are generally not designed for older adults, since they are mostly not considered to be at risk of acquiring or transmitting HIV through sexual contact.

Immunological and Virological Parameters

Following seroconversion, older patients suffer from more rapid disease progression with a steeper decline of CD4 cell counts as compared to younger patients [2]. The hazard ratio for death is twice as high in older patients [28]. As a consequence, current guidelines have been adapted to risk groups and now recommend earlier treatment at higher CD4 cell counts for older patients [9]. Patients in our cohort were treated before the release of these guidelines and we observed the opposite trend of delayed treatment in older patients: the median CD4 cell count at the start of treatment was lower in older patients than in younger patients (176 vs. 200/ μl , $p = 0.017$). It was previously shown that a lower CD4 cell nadir at the start

of ART was a predictor for increased mortality [3, 4, 13, 20]. Thus, our data demonstrate that older patients were in fact disadvantaged with regard to optimal care in the past, highlighting the need for improved care of older patients through earlier initiation of ART.

Thymic function decreases with age, and HIV infection leads to an additional impairment of thymic cell output that can be measured in the peripheral blood and lymphoid tissues [10, 16]. After initiation of ART, disease progression and mortality depend on age and immunological reconstitution [19, 24]. Overall mortality was increased among patients who failed to obtain a normal CD4+ T cell count while on therapy [21]. An important strength of our cohort is the large number of follow-up events that allow the evaluation of immunological and virological response to treatment in different age groups. We could show that CD4 cell reconstitution after 72 weeks of ART was smaller in older than in younger patients, demonstrating that immune recovery is strongly dependent on age. In analogy to our findings, an inverse relationship between older age and maximum CD4 cell response to ART was confirmed in the EuroSida study and in a French cohort [12, 37]. The impaired immunological response may explain the higher risk of clinical progression in older patients [12].

Taken together, a more rapid CD4 cell decline after seroconversion, a delayed start of ART and a compromised immune recovery under ART impair the prognosis of older patients with HIV.

CDC Stage at Baseline

It remains a matter of debate whether the increase in HIV infection diagnoses in patients above 50 is due to more HIV late presenters or is driven by infections newly acquired above the age of 50 [7, 15, 22, 32]. It has been found that patients over the age of 50 at risk for HIV do not routinely get tested and older age is associated with increased odds of a late diagnosis and short-term mortality [5, 7]. In a recent study by Smith et al. [32] the number of late presenters was higher in older patients as compared to younger patients (48 vs. 33%). Equally, data from the CDC show that patients diagnosed with HIV at older age were more often diagnosed with advanced disease and AIDS-defining conditions (CDC HIV/AIDS Surveillance Report, 2006; <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/index.htm>). In a survey by Smith et al. [32] approximately half of the older patients were late presenters and the other half had acquired HIV beyond 50 years. In the present analysis, older patients were significantly more often started on

ART in advanced CDC stages B and C as compared to younger patients (74.4 vs. 55.5%), indicating a high number of late presenters among older patients in our cohort. It was shown that the short-term mortality of late presenters beyond the age of 50 was significantly higher as compared to either younger adults or older adults who were not diagnosed late [31, 32]. Thus, every effort should be made to improve the prognosis by establishing an earlier diagnosis in older HIV-infected patients. As a first step, the possibility of an HIV infection must be considered more frequently in older patients and health care providers should explicitly broach different aspects of sexual behavior during counseling/conversation. A survey of new HIV diagnoses in the UK and Ireland showed that many opportunities for earlier diagnosis are missed, because in older patients HIV-associated comorbidities were often misinterpreted as age-related conditions [35].

Response to Treatment

In our cohort, the group of older patients started ART at more advanced CDC stages than younger patients and more frequently underwent changes of ART (table 1). These unfavorable characteristics make the elderly HIV population a major problematic group for decreased tolerability with increased adverse events. For example, Knobel et al. [18] showed that side effects caused by protease inhibitor (PI)-based antiretroviral regimen were more frequent among older patients above 60 as compared to younger patients (64 vs. 35%, $p = 0.001$). PIs are predominantly metabolized by the liver. It may be hypothesized that decreased tolerability of PIs is triggered by frequent compromise of the hepatic function in older age.

In our study, the virological response to treatment was comparable in younger and older patients and there was a similar duration of the first-line regimen in both groups. It was hypothesized that older patients might have a greater understanding of medical treatments and generally suffer less from stress. Both factors may relate to improved adherence [27, 38, 39].

Conclusions

The results from this large cohort of treatment-naïve patients provide insight into the epidemiology of HIV in the elderly. A number of unfavorable characteristics turn the older HIV population into a major problematic group for optimization of HIV prevention and treatment strategies. Testing for HIV infection should be more vigorous-

ly pursued in older adults at risk for HIV and specific prevention programs are needed. At the same time, the negative prognostic consequences of an undiagnosed or untreated HIV infection are increased in the older HIV-infected population. Thus, ART should be offered at earlier time points with higher CD4 cell counts to prevent clinical progression as well as the spread of the infection.

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References

- 1 AIDS among persons aged greater than or equal to 50 years – United States, 1991–1996. *Morb Mortal Wkly Rep* 1998;47:21–27.
- 2 CASCADE Collaboration: Differences in CD4 cell counts at seroconversion and decline among 5739 HIV-1-infected individuals with well-estimated dates of seroconversion. *J Acquir Immune Defic Syndr* 2003;34: 76–83.
- 3 Antiretroviral Therapy Cohort Collaboration: Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008;372:293–299.
- 4 Baker JV, Peng G, Rapkin J, Abrams DI, Silverberg MJ, MacArthur RD, Cavert WP, Henry WK, Neaton JD: CD4+ count and risk of non-AIDS diseases following initial treatment for HIV infection. *AIDS* 2008;22:841–848.

- 5 CASCADE Collaboration: Differences in CD4 cell counts at seroconversion and decline among 5739 HIV-1-infected individuals with well-estimated dates of seroconversion. *J Acquir Immune Defic Syndr* 2003;34:76–83.
- 6 Castilla J, Sobrino P, De La Fuente L, Noguer I, Guerra L, Parras F: Late diagnosis of HIV infection in the era of highly active antiretroviral therapy: consequences for AIDS incidence. *AIDS* 2002;16:1945–1951.
- 7 Chadborn TR, Baster K, Delpech VC, Sabin CA, Sinka K, Rice BD, Evans BG: No time to wait: how many HIV-infected homosexual men are diagnosed late and consequently die? (England and Wales, 1993–2002). *AIDS* 2005;19:513–520.
- 8 Chiao EY, Ries KM, Sande MA: AIDS and the elderly. *Clin Infect Dis* 1999;28:740–745.
- 9 Clumeck N, Pozniak A, Raffi F: European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. *HIV Med* 2008;9:65–71.
- 10 Douek DC, McFarland RD, Keiser PH, Gage EA, Massey JM, Haynes BF, Polis MA, Haase AT, Feinberg MB, Sullivan JL, Jamieson BD, Zack JA, Picker LJ, Koup RA: Changes in thymic function with age and during the treatment of HIV infection. *Nature* 1998;396:690–695.
- 11 el-Sadr W, Gettler J: Unrecognized human immunodeficiency virus infection in the elderly. *Arch Intern Med* 1995;155:184–186.
- 12 Grabar S, Kousignian I, Sobel A, Le BP, Gasnault J, Enel P, Jung C, Mahamat A, Lang JM, Costagliola D: Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS* 2004;18:2029–2038.
- 13 Grabar S, Pradier C, Le Corfec E, Lancar R, Allavena C, Bentata M, Berlureau P, Dupont C, Fabbro-Peray P, Poizot-Martin I, Costagliola D: Factors associated with clinical and virological failure in patients receiving a triple therapy including a protease inhibitor. *AIDS* 2000;14:141–149.
- 14 Grimes RM, Otiniano ME, Rodriguez-Barradas MC, Lai D: Clinical experience with human immunodeficiency virus-infected older patients in the era of effective antiretroviral therapy. *Clin Infect Dis* 2002;34:1530–1533.
- 15 Jansen K, Brockmeyer NH, Hahn M, Kaul I, Fenske S, Rausch M, Kuhlmann B, Ulmer A, Lauenroth-Mai E, Harrer T, Hower M, Skaletz-Rorowski A, Michalik C: Epidemiological composition, clinical and treatment characteristics of the patient cohort of the German Competence Network for HIV/AIDS. *Eur J Med Res* 2009;14:415–425.
- 16 Kalayjian RC, Landay A, Pollard RB, Taub DD, Gross BH, Francis IR, Sevin A, Pu M, Spritzler J, Chernoff M, Namkung A, Fox L, Martinez A, Waterman K, Fiscus SA, Sha B, Johnson D, Slater S, Rousseau F, Lederman MM: Age-related immune dysfunction in health and in human immunodeficiency virus (HIV) disease: association of age and HIV infection with naive CD8+ cell depletion, reduced expression of CD28 on CD8+ cells, and reduced thymic volumes. *J Infect Dis* 2003;187:1924–1933.
- 17 Klotz U: Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev* 2009;41:67–76.
- 18 Knobel H, Guelar A, Valdecillo G, Carmona A, Gonzalez A, Lopez-Colomes JL, Saballs P, Gimeno JL, Diez A: Response to highly active antiretroviral therapy in HIV-infected patients aged 60 years or older after 24 months follow-up. *AIDS* 2001;15:1591–1593.
- 19 Lanoy E, May M, Mocroft A, Phillip A, Justice A, Chene G, Furrer H, Sterling T, Monforte AD, Force L, Gill J, Harris R, Hogg RS, Rockstroh J, Saag M, Khaykin P, de Wolf F, Sterne JA, Costagliola D: Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements. *AIDS* 2009;23:2199–2208.
- 20 Le Moing V, Chene G, Carrieri MP, Alioum A, Brun-Vezinet F, Piroth L, Cassuto JP, Moatti JP, Raffi F, Lepout C: Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. *AIDS* 2002;16:21–29.
- 21 Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, Pellegrin JL, Katlama C, Dabis F, Lepout C: HIV-infected adults with a CD4 cell count greater than 500 cells/mm³ on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr* 2007;46:72–77.
- 22 Mack KA, Ory MG: AIDS and older Americans at the end of the twentieth century. *J Acquir Immune Defic Syndr* 2003;33(suppl 2):S68–S75.
- 23 Manfredi R, Chiodo F: A case-control study of virological and immunological effects of highly active antiretroviral therapy in HIV-infected patients with advanced age. *AIDS* 2000;14:1475–1477.
- 24 May M, Sterne JA, Sabin C, Costagliola D, Justice AC, Thiebaut R, Gill J, Phillips A, Reiss P, Hogg R, Ledergerber B, D'Arminio MA, Schmeisser N, Staszewski S, Egger M: Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies. *AIDS* 2007;21:1185–1197.
- 25 Oette M, Reuter S, Kaiser R, Lengauer T, Fätkenheuer G, Knechten H, Hower M, Pfister H, Häussinger D, RESINA Study Group: Epidemiology of transmitted drug resistance in chronically HIV-infected patients in Germany: the RESINA Study 2001–2009. *Intervirology* 2012;55:154–159.
- 26 Orchi N, Balzano R, Scognamiglio P, Navarra A, De Carli G, Elia P, Grisetti S, Sampaiolesi A, Giuliani M, De Filippis A, Puro V, Ippolito G, Girardi E: Ageing with HIV: newly diagnosed older adults in Italy. *AIDS Care* 2008;20:419–425.
- 27 Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, van Lunzen J, Katzenstein TL, Antunes F, Lundgren JD, Clotet B: Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Arch Intern Med* 2000;160:1123–1132.
- 28 Perez JL, Moore RD: Greater effect of highly active antiretroviral therapy on survival in people aged > or =50 years compared with younger people in an urban observational cohort. *Clin Infect Dis* 2003;36:212–218.
- 29 Skiest DJ, Keiser P: Human immunodeficiency virus infection in patients older than 50 years. A survey of primary care physicians' beliefs, practices, and knowledge. *Arch Fam Med* 1997;6:289–294.
- 30 Skiest DJ, Rubinstein E, Carley N, Gioiella L, Lyons R: The importance of comorbidity in HIV-infected patients over 55: a retrospective case-control study. *Am J Med* 1996;101:605–611.
- 31 Smith C, D:A:D Study Group: Association between modifiable and non-modifiable risk factors and specific causes of death in the ART era: the data collection on adverse events of anti-HIV drugs study. 16th Conference on Retroviruses and Opportunistic Infections (abstract 145), Montréal, 2009.
- 32 Smith RD, Delpech VC, Brown AE, Rice BD: HIV transmission and high rates of late diagnoses among adults aged 50 years and over. *AIDS* 2010;24:2109–2115.
- 33 Stall R, Catania J: AIDS risk behaviors among late middle-aged and elderly Americans. The National AIDS Behavioral Surveys. *Arch Intern Med* 1994;154:57–63.
- 34 Suligoi B, Boros S, Camoni L, Lepore D: Aggiornamento dei casi di AIDS notificati in Italia e delle nuove diagnosi di HIV al 31 Dicembre. *Not Ist Super Sanità* 2005;18 (suppl 1).
- 35 Sullivan AK, Curtis H, Sabin CA, Johnson MA: Newly diagnosed HIV infections: review in UK and Ireland. *BMJ* 2005;330:1301–1302.
- 36 Tumbarello M, Rabagliati R, De Gaetano DK, Bertagnolio S, Tamburrini E, Tacconelli E, Cauda R: Older HIV-positive patients in the era of highly active antiretroviral therapy: changing of a scenario. *AIDS* 2003;17:128–131.
- 37 Viard JP, Mocroft A, Chiesi A, Kirk O, Røge B, Panos G, Vetter N, Bruun JN, Johnson M, Lundgren JD: Influence of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis* 2001;183:1290–1294.
- 38 Wellons MF, Sanders L, Edwards LJ, Bartlett JA, Heald AE, Schmader KE: HIV infection: treatment outcomes in older and younger adults. *J Am Geriatr Soc* 2002;50:603–607.
- 39 Wutoh AK, Elekwachi O, Clarke-Tasker V, Daftary M, Powell NJ, Campusano G: Assessment and predictors of antiretroviral adherence in older HIV-infected patients. *J Acquir Immune Defic Syndr* 2003;33(suppl 2):S106–S114.