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ORIGINAL RESEARCH

Does European or non-European origin influence health care and prognosis for HIV patients in Europe?

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Background

Previous studies, especially in North America, have shown that socio-economic factors may influence the prognosis for patients with HIV. This study was performed in order to determine if European or non-European origin influence provision of health-care and survival among HIV patients in Europe.

Methods

Fifty HIV clinics in 17 European countries are involved in a European prospective, observational multicentre study. In total, 7230 consecutive patients with HIV attending a routine clinic visit were included in the study. Data on demographics, treatment and laboratory results were collected at time of recruitment into the study and thereafter every 6 months.

Results

The median $CD4^+$ lymphocyte count at AIDS diagnosis was 60/mm^3, and was similar for all ethnic groups ($P = 0.87$, Kruskall–Wallis test). The median terminal $CD4^+$ lymphocyte count was 17/mm^3 and, again, there was no significant difference between continents of origin ($P = 0.35$, Kruskall–Wallis test). Antiretroviral drugs were initiated at similar median $CD4^+$ lymphocyte counts and there was no statistically significant difference in survival after a diagnosis of AIDS.

Conclusions

AIDS was diagnosed at the same level of immunodeficiency independent of European or non-European origin and antiretroviral drugs were provided at similar levels of immunodeficiency. No differences in survival depending on continent of origin was found. In spite of these encouraging findings concerns remain that belonging to an ethnic minority can be an obstacle in getting into contact with treatment facilities and thus benefiting from developments in the management of HIV.

Key words: AIDS, HIV, ethnicity, health-care, race

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Introduction

Studies in western Europe have shown higher general risks of morbidity and mortality in people from lower socio-economic groups [1]. Studies in North America and elsewhere looking specifically at patients infected with HIV have shown differences in survival depending on access to care [2,3], race [4,5] and socio-economic status [6–8]. Hispanics, blacks and patients from a lower socio-economic group have been shown to have a poorer prognosis, although some studies have suggested no differences in prognosis [9–11]. Any observed differences have usually been attributed to poor access to medical services, lack of insurance and other socio-economic factors [12–14], rather than any biological or racial differences [15,16].

We were interested to see if it was possible to demonstrate a difference in morbidity and mortality among HIV patients according to origin across Europe. A relatively high proportion of patients with HIV in Europe originate

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from poor countries with a high prevalence of HIV [17]. Reasons for not having access to health care can be many; economic, logistical, legislative, social and psychological. This issue is becoming increasingly important given the rapidly changing treatment options which are now available to treat patients with HIV.

The aim of this study was therefore to investigate differences in access to healthcare and prognosis in patients from minority ethnic origins; in particular, to determine if such patients were first seen for HIV at a more advanced disease stage, had equal access to treatment and experienced similar survival when compared to that of a native European population.

Methods

Patients

EuroSIDA is an ongoing prospective, observational study of currently 7230 patients at 50 HIV clinics in 17 different European countries, including Israel (see Appendix). Details of the study design have been published elsewhere [18,19]. Patients were recruited in three cohorts in 1994, 1996 and 1997, respectively. The aim was to recruit a cross-section of HIV patients in Europe. Eligible patients were those older than 16 years who had a $CD4^+$ count of < 500 within 4 months prior to recruitment. Also, the patient had to have been booked for a regular visit to the clinic at least 2 weeks in advance. At each centre a predefined number of patients fulfilling the inclusion criteria were to be recruited. Commencing on a predefined starting date, consecutive eligible patients were included until this predefined number of patients were enrolled at each centre. Information was collected during the visit from patient case notes and by patient interview and entered onto a standardized data collection form. The information compiled included age, gender, mode of transmission, country of origin, race, date of HIV diagnosis, CD4 counts, treatment history (antiretrovirals and treatment/prophylaxis for opportunistic infections), opportunistic infections and malignancies. Thereafter information on treatment, clinical condition and laboratory markers were collected every 6 months. Information on all AIDS-defining illnesses was collected and diagnosed using the 1993 clinical definition from the Centers for Disease Control [20]. Data were checked for logistical errors by the co-ordinating centre, and all major centres were visited to ensure correct patient inclusion and accurate data recording.

In order to make regional comparisons possible the participating European centres were arbitrarily divided into the regions north, central and south, as described in Table 1. Our interest was to investigate if ethnicity influenced provision of health care and prognosis. Ethnicity and race can be defined in many ways. To ensure unambiguous criteria we defined ethnicity according to country of birth. We compared those patients who were born in Asia or Africa to patients who were born in a participating or other European country. This would ensure that first-generation migrants from poor countries in Africa and Asia were separate from the native European population. For 202 patients the country of birth was not available. These patients, as well as 163 patients born in the Americas, were not included in the comparisons and are referred to in the tables as 'other'. At inclusion into the study the investigator also classified each participant according to 'race' as 'white', 'black', 'Asian' or 'other'. This information was used in a subset of the analysis.

Statistical methods

Patient follow-up was measured as the time between recruitment to EuroSIDA and the date of death, or last follow-up visit for those patients who were not known to have died. Similarly, duration of treatment was measured either as the time between starting and stopping treatment, or for those patients who remained on treatment at their last visit, as the time between starting treatment and last follow-up.

Continuous variables, such as age and $CD4^+$ lymphocyte count at study recruitment, were generally not normally distributed, hence non-parametric tests such as the Wilcoxon signed rank test were used to test for differences between the groups. Categorical variables were compared using the χ^2 test. The $CD4^+$ lymphocyte count at AIDS, start of treatment or at enrolment to EuroSIDA was the nearest measurement to the date in question. In 393 patients the nearest measurement was not within 3 months of the event; these patients were excluded from that particular analysis. The terminal $CD4^+$ lymphocyte count was the last recorded $CD4^+$ lymphocyte count before death, and within 3 months of the event.

Standard Kaplan–Meier curves [21] were used to explore the differences in survival after an AIDS diagnosis in African or Asian patients compared to Europeans. Patients who were diagnosed with AIDS prior to recruitment in EuroSIDA were excluded from this analysis; that is, only incident AIDS cases were included to minimize the bias caused by the inclusion of retrospective data.

Cox proportional hazard models were used to calculate the relative hazard of death [22]. Diagnosis of AIDS and the logarithm of the latest $CD4^+$ lymphocyte count were

Table 1 Basic characteristics of the patients included in EuroSIDA, by origin

		Total		Europe		Africa		Asia		Other or unknown		
		N	%	*N*	%	*N*	%	*N*	%	*N*	%	*P*-value
All patients		7230	100	6316	87.4	464	6.4	85	1.2	365	5.1	
Exposure	HS	3316	45.9	3074	48.7	32	6.9	39	45.9	171	46.9	0.001
Category	IDU	1819	25.2	1737	27.5	11	2.4	5	5.9	66	18.1	
	HT	1620	22.4	1142	18.1	347	74.8	35	41.2	96	26.3	
	Other	475	6.6	363	5.8	74	16.0	6	7.1	32	8.8	
Gender	Male	5724	79.3	5139	81.4	231	49.8	63	75.9	291	79.7	0.001
	Female	1499	20.7	1172	18.6	233	50.2	20	24.1	74	20.3	
Time of AIDS	No AIDS	4127	57.1	3535	56.0	311	67.0	56	65.9	225	61.6	0.001
in relation to	Before	2171	30.0	1919	30.4	118	25.4	23	27.1	111	30.4	
to study period	During	932	12.9	862	13.7	35	7.5	6	7.1	29	8.0	
Deaths	No	5863	81.1	5050	80.0	420	90.5	75	88.2	318	87.1	0.001
	Yes	1367	18.9	1266	20.0	44	9.5	10	11.8	47	12.9	
Region*	South	2489	34.4	2304	36.5	111	23.9	10	11.8	64	17.5	0.001
	Central	2284	31.6	1911	30.3	168	36.2	34	40.0	171	46.9	
	North	2457	34.0	2101	33.3	185	39.9	41	48.2	130	35.6	
Cohort	I	3122	43.2	1711	44.7	159	24.3	27	31.8	114	31.2	0.001
	II	1369	18.9	1234	19.5	89	19.2	12	14.1	34	9.3	
	III	2739	37.9	2260	35.8	216	46.6	46	54.1	217	59.5	

HS; homosexual, IDU; intravenous drug user, HT; heterosexual. *South: Greece, Israel, Italy, Portugal, Spain. Central: Austria, Belgium, France, Germany (south), Luxembourg, Switzerland. North: Denmark, Germany (north), Ireland, Netherlands, Norway, Sweden, United Kingdom.

included in the Cox model as time-dependent covariates. Adjustment for treatment was not made here as the aim of the study was to elucidate possible differences in given care linked to origin.

All tests of significance in this analysis are two-sided. Tests of the proportional hazards assumption revealed that there was no evidence for non-proportionality ($P > 0.2$). All statistical analyses were performed using SAS [23].

Results

Of 7230 patients recruited to EuroSIDA, 6316 (87.4%) were born in one of the 17 countries involved in the study or another European country, 464 (6.4%) were born in Africa and 85 (1.2%) in Asia. The countries with the highest proportion of patients from Africa or Asia were Israel (40.8%), Belgium (26.0%), Sweden (20.1%) and Norway (10.5%). Origin was correlated to race (white, black, Asian or other). Among patients born in Europe, 97.6% were described as 'white', 84.9% of patients from Africa as 'black' and 64.7% of patients from Asia were racially classified as 'Asian'.

There was considerable heterogeneity between patients included in this study, as shown in Table 1, which describes the patients overall and according to origin, together with a *P*-value which compares the distribution of patients according to various demographic factors. Patients born in Africa or Asia were significantly more likely to have acquired their infection through heterosexual contact ($P < 0.001$, χ^2 test), were more likely to be female ($P < 0.001$, χ^2 test) and were more likely to reside in Northern Europe ($P < 0.001$, χ^2 test). In addition, patients from Africa or Asia were less likely to have AIDS when they were recruited to EuroSIDA ($P < 0.001$, χ^2 test) or to have died during follow-up ($P < 0.001$, χ^2 test).

The median age at recruitment to EuroSIDA was 36.0 years (90% range 25.8–56.0 years); 80% of the patients were aged below 45 years at recruitment. There were significant differences in age at recruitment according to origin; patients born in Africa (median age 33.7 years) and Asia (median age 35.2 years) were significantly younger at recruitment than other patients ($P = 0.0001$, Kruskall–Wallis test). There were no differences in the median duration of follow-up (median 12 months, 90% range 0.0–43.0 months) according to origin, nor in the proportion of patients with less than 3 months of follow-up ($P = 0.12$, χ^2 test). The median $CD4^+$ lymphocyte count at recruitment to EuroSIDA was 206/mm^3, and was significantly higher among patients born in Africa (median 214/mm^3) and patients born in Asia (median 252/mm^3) when compared with patients from Europe (median 202/mm^3, $P = 0.0018$, Kruskall–Wallis test).

Table 2 Provision of antiretroviral treatment across origins

		All patients	Europe	Africa	Asia	Other or unknown	*P*-value
ZDV	No. (%)	1040 (14.4)	899 (14.2)	70 (15.1)	11 (12.9)	60 (16.4)	0.47
	Yes: before enrolment (%)	5235 (72.4)	4588 (72.6)	326 (70.3)	58 (68.2)	263 (72.1)	
	Yes: after enrolment (%)	955 (13.2)	829 (13.1)	68 (14.7)	16 (18.8)	42 (11.5)	
	Median CD4 at starting	209	208	192	238	231	0.098
	Median duration treatment	25.0	25.0	23.5	21.0	20.0	0.011
	Median date started	3/94	2/94	11/94	9/95	7/94	0.0001
3TC	No. (%)	2742 (37.9)	2439 (38.6)	163 (35.1)	25 (29.4)	115 (31.5)	0.001
	Yes: before enrolment (%)	1845 (25.5)	1532 (24.3)	137 (29.5)	31 (36.5)	145 (39.7)	
	Yes: after enrolment (%)	2643 (36.6)	2345 (37.1)	164 (35.3)	29 (34.1)	105 (28.8)	
	Median CD4 at starting	182	180	184	262	205	0.040
	Median duration treatment	12.0	12.0	12.0	14.0	10.5	0.0016
	Median date started	10/96	10/96	10/96	8/96	9/96	0.051
IND	No. (%)	4750 (65.7)	4195 (66.4)	280 (60.3)	46 (54.1)	229 (62.7)	0.001
	Yes: before enrolment (%)	769 (10.6)	616 (9.8)	67 (14.4)	17 (20.0)	69 (18.9)	
	Yes: after enrolment (%)	1711 (23.7)	1505 (23.8)	117 (25.2)	22 (25.9)	67 (18.4)	
	Median CD4 at starting	165	167	141	234	140	0.073
	Median duration treatment	8.0	8.0	8.0	8.0	6.5	0.25
Median date started		12/96	12/96	1/97	1/97	11/96	0.12

ZDV, zidovudine; 3TC, lamivudine; IND, indinavir.

$CD4^+$ lymphocyte count at AIDS and the last $CD4^+$ lymphocyte count prior to death ('terminal' $CD4^+$ lymphocyte count) was calculated both overall and according to origin. The median $CD4^+$ lymphocyte count at AIDS diagnosis was 60/mm^3 (90% range 5–345/mm^3), and was similar for all groups ($P = 0.87$, Kruskall–Wallis test). A $CD4^+$ lymphocyte count within 3 months of death was available for 1361 patients (99.6%). The median terminal $CD4^+$ lymphocyte count was 17/mm^3 and, again, there was no significant difference between the groups ($P = 0.35$, Kruskall–Wallis test), although the numbers of patients in some groups were small, which may limit the power to detect any differences.

Introduction of anti retroviral therapy

In Table 2, introduction of zidovudine, lamivudine and indinavir was compared between patients with different origins; the *P*-values compare the proportion of patients starting therapy or the date and CD4 lymphocyte count of starting therapy according to origin. There were no major or systematic differences in the proportion of patients receiving treatment either before or after recruitment to EuroSIDA, nor were there any major differences in the median $CD4^+$ lymphocyte count at initiation of treatment, duration of treatment or calendar month and year of starting treatment. There was, however, a tendency towards earlier initiation of therapy in patients born in Asia. Investigations were also performed for initiation of *Pneumocystis carinii* pneumonia prophylaxis and for participation in clinical trials with similar results (data not presented).

Survival after AIDS

Figure 1 illustrates survival after a diagnosis of AIDS among 895 patients who were diagnosed with AIDS after recruitment to EuroSIDA, 472 of whom have died (52.7%). Another eight patients with AIDS of European origin were not included in the survival analysis as there was no follow-up subsequent to the AIDS diagnosis. Of the 895 patients, 854 originated from Europe and 41 from Africa or Asia. Because of small numbers, we have combined patients born in Africa and Asia to compare to patients born in Europe. There were no statistically significant differences in survival ($P = 0.32$, log-rank test). Median survival among patients originating from Europe was 21 months (95% confidence interval 19–23 months) compared to 17.1 months (95% confidence interval 9–27 months) for patients originating from Africa/Asia. At 12 months the proportion of patients originating from Africa/Asia who had died compared to European patients was 38.7 and 35.9%, respectively.

Risks for death

Table 3 presents a Cox proportional hazards model, the relative risks for death among all HIV patients and 95% confidence intervals. In the univariate analysis, patients born in Africa have a statistically significant lower relative

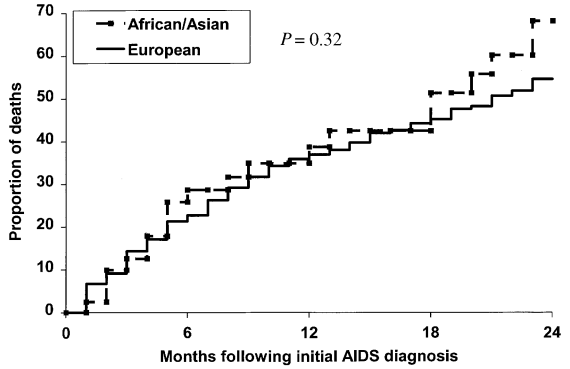

Fig. 1 Survival after an AIDS diagnosis.

Table 3 Relative risk of death for HIV patients in groups with different origins using the Cox proportional hazards models

	Relative hazard	95% confidence interval	*P*-value
Univariate			
European	1.00	–	–
African	0.51	0.37–0.68	0.0001
Asian	0.66	0.35–1.22	0.19
Other	0.91	0.68–1.22	0.55
Multivariate			
European	1.00	–	–
African	0.80	0.56–1.15	0.22
Asian	1.18	0.59–2.36	0.65
Other	1.24	0.90–1.71	0.18

In the multivariate analysis adjustment is made for age, gender, risk group, region of Europe, CD4 count, and cohort.

risk of dying when compared to patients born in Europe (relative hazard rate 0.51, 95% confidence interval 0.37–0.68, *P*-value = 0.0001). There was, however, no difference when patients born in Asia were compared to patients born in Europe. In the multivariate analysis where adjustment is made for important confounding variables such as age, region of Europe, $CD4^+$ count and cohort (time of inclusion into study) no differences remain between the groups.

Discussion

In this study of 7230 HIV patients, with a median duration of follow-up of 12 months at different HIV clinics in 17 European countries, we were unable to demonstrate any significant differences in medical services or outcome for patients depending on their ethnic background defined from country of birth.

$CD4^+$ lymphocyte count at enrolment into the study was similar regardless of origin. This refutes a possible belief that immigrants from poor countries would present at the centres in a more advanced stage of the disease. Furthermore, no differences were seen in the proportion lost to follow-up, indicating that the clinics were able to provide continued contact with the patients.

Antiretroviral therapy

We chose to study specifically the introduction of three antiretroviral drugs: zidovudine, lamivudine and indinavir. Zidovudine was chosen because it was the first licensed antiretroviral therapy; when combination therapy was found to be superior to single therapy lamivudine was usually added to existing medication; and during the study period indinavir was the most frequently used initial protease inhibitor across Europe. Introduction of these measures seems, from our results, to be guided by the clinical condition regardless of ethnicity. However, the number of migrants, especially those originating from Asia, was small, which may have limited the power to detect differences.

Survival after AIDS

Once an AIDS-defining condition had developed, we found no differences in the survival or the $CD4^+$ count at which the patient died. Again, the number of deaths among people from Africa/Asia was low, making the confidence intervals broad. This relatively good prognosis for AIDS patients of African and Asian origin stands in contrast to what has been described from, for instance, Africa where a rapid progression to death has been reported [24]. Many factors can play a role here. Malnutrition, a relative abundance of possible pathogens and concomitant infections as well as the lack of drugs for the treatment of HIV and opportunistic infections may be important. A recent study comparing outcome for African and non-African HIV patients in London was similarly unable to identify African origin as a negative prognostic factor [25]. This lack of difference compared to findings in North America could be due to more equal access to care in publicly funded health-care systems.

Representation of ethnic minorities

There are some factors which differentiate immigrants from native Europeans. A major difference is that heterosexual transmission is more common among immigrants, while European patients have acquired their infection predominantly through homosexual contact or intravenous drug use (IDU). It has been argued that the prognosis of IDUs

with HIV differs from that of other exposure categories [26,27], so we repeated our analyses excluding IDUs. The results we obtained were very similar (data not shown). The migrant population also accounted for a larger proportion of the patients in northern Europe compared to the south. Controlling for region in Europe did not alter the findings. As stated earlier, race is closely linked to continent of origin. Repeating the various analyses including only 'white' Europeans, 'black' Africans and 'Asian' Asians did not change the conclusions. In spite of this, place of birth remains a broad criterion for defining socio-economic status.

There are some possible biases in this study which should be considered. One crucial question is to what degree the results from this study can be generalized to patients with HIV in Europe at large. Patients recruited into EuroSIDA are from specialist clinics, which have a great deal of expertise in caring for patients with HIV. Such centres may have earlier access to new treatments and patients may select themselves to attend such a clinic. Patients from minority ethnic groups who attend these centres may not be representative of minority ethnic groups across Europe. One obvious reason for the lack of differences shown could be that migrants from poor countries never arrived at the centres for treatment of their HIV infection and were therefore not included in our study. Approximately 30% of patients in Europe with HIV contracted through heterosexual contact are estimated to be associated with 'pattern II' countries ('cases originating from, residing in or having a partner originating from a country where heterosexual transmission is frequent') [17]. In the EuroSIDA study, there were 549 people born in Africa or Asia. Of these, 382 have been classified as infected through heterosexual contact. The total number of people infected through heterosexual contact was 1620; thus 24% of the heterosexual patients have originated from Africa or Asia. The proportion of patients originating from Africa and Asia in the study is therefore comparable to that found in Europe as a whole. Also, some countries within Europe had a much higher proportion of migrants than others. We repeated our analysis separately for the four countries with the highest proportion of patients born in Africa or Asia, with very similar findings (data available from the author on request).

Earlier work from the EuroSIDA study group [19] has discussed the possibility of a potential selection bias against the recruitment of patients with end-stage disease. In some countries, patients with end-stage disease may be discharged to hospice care rather than general out-patient clinic follow-up and therefore would not be recruited into the study, while in some countries the opposite may be the case. The mortality rate of patients in EuroSIDA was very low during the first 3 months of this study so the Cox analysis was repeated, excluding patients who had less than 3 months of follow-up. The results remained very similar to those presented (data available from author on request).

Studies on selected groups in Africa have shown a more rapid progression to AIDS compared to what has been observed in Europe and North America. It has been speculated that a higher exposure to pathogens in poor countries with over-activation of the immune system can make the host both more susceptible to HIV and less capable of coping with it [28]. If this is true it seems that this effect no longer prevails among immigrants to Europe, or that the effect is counterbalanced by other factors. No indication of a different response to the infection was seen in this study.

Need for community-based investigations

This study, comparing treatment and outcome for HIV patients in Europe, was unable to demonstrate any difference in treatment or outcome for patients depending on continent of birth. Studies are needed in order to determine to what extent there are members of vulnerable ethnic communities who are infected with HIV who do not have their infection diagnosed and do not reach treatment facilities. The finding in this study that patients of non-European origin seem to gain equally well from the services at the health centres make it the more compelling to ensure that minority populations are given possibilities to benefit from developments in the management of HIV.

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Appendix

The multicentre study group on EuroSIDA (national co-ordinators in parentheses).

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Firenze; B. DeRienzo, Catania, Università di Modena, Modena; A. Chirianni, Montesarchio, Presidio Ospedaliero 'D. Cotugno', Napoli; F Sorice, Santopadre, Università di Roma 'La Sapienza', Rome; V. Giannini, Franci, P. Narciso, Campitelli, M.A. Rosci, Zaccarelli, Ospedale Spallanzani, Rome; A. Lazzarin, R. Finazzi, Ospedale San Raffaele, A. D'Arminio Monforte, Osp. L. Sacco, Milano. *Luxembourg* (R. Hemmer), T. Staub, Centre Hospitalier, Luxembourg. *Netherlands* (P. Reiss), Academisch Ziekenhuis bij de Universitet van Amsterdam. *Norway* (J. Bruun), Ullevål Hospital, Oslo. *Portugal* (F. Antunes), Hospital Santa Maria, K. Mansinho, Hospital de Egas Moniz, R. Proenca, Hospital Curry Cabral, Lisbon. *Spain* (J. González-Lahoz), R. Polo, Instituto Carlos III, Madrid; B. Clotet, A. Jou, J. Conejero, D. Tural, Hospital Germans Trias i Pujol, Badalona; J. Gatell, J. Miró, Hospital Clinic I Provincial, Barcelona. *Sweden* (A. Blaxhult), Karolinska Hospital, B. Heidemann, Södersjukhuset, P. Pehrson, Huddinge Sjukhus, Stockholm. *Switzerland* (B. Ledergerber), R. Weber, University Hospital, Zürich; P. Francioli, Centre Hospitalier Universitaire Vaudois, Lausanne; B. Hirschel, P. Sudre, Hospital Cantonal Universitaire de Geneva, Geneva. *United Kingdom* (S. Barton), St Stephen's Clinic, Chelsea and Westminster Hospital; A. Johnson, D. Mercy, University College London Medical School; M. Johnson, A. Mocroft, A. Phillips, C. Loveday, Royal Free Hospital School of Medicine; A. Pinching, Medical College of St Bartholomew's Hospital, London; R. Brettle, City Hospital, Edinburgh.
Steering committee: J. Nielsen (chair), N. Clumeck, M. Dietrich, J. Gatell, A Johnson, C Katlama, B. Ledergerber, C. Loveday, A. Phillips, P. Reiss, S. Vella.
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