IMIT AMACS ECS-Mothers & ECS-Infants NSHPC-Mothers & NHPS-Infants PISCIS KOMPNET CASCADE ANRS CO2 SEROCO Frankfurt HIV-Cohort Study San Raffaele ANRS CO1/CO10 EPF UK CHIC Athena ITLR-Mothers & ITLR-Infants Swiss HIV Cohort Study ICC ANRS CO6 PRIMO Co-RIS MOCHIV-Mothers & MoCHIV-Infants The Italian MASTER Cohort CHIPS ANRS CO4 French Hospital's Database on HIV HIV-MIP-Mothers & HIV-MIP-Infants GEMES-Haemo ANRS CO3 AQUITAINE EuroSIDA Madrid Cohort HIV Children VACH Modena Cohort Study Danish HIV Study ANRS CO8 COPILOTE ICONA St. Pierre

Collaboration of Observational HIV Epidemiological Research Europe

Coordination: Copenhagen HIV Programme (CHIP) & Institut de Santé Publique, d'Epidémiologie et de Développement (ISPED)

Response to combination antiretroviral therapy (cART): variation by age

Caroline A Sabin for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Study
Royal Free & University College Medical School, London, UK

Contact: Caroline A Sabin
Address: Department of Primary Care and Population Sciences, Royal Free & UC Medical School, Rowland Hill Street, London NW3 2PF, UK
Tel: 0044 207 830 2239 ext. 34752
Fax: 0044 207 7941224
E-mail: c.sabin@pcps.ucl.ac.uk

Poster 528

BACKGROUND

- World wide, around 15% of HIV-infected individuals requiring therapy are children and an increasing proportion of adults are aged >50 years
- The majority of individuals in cART-outcome studies have been aged between 18 and 50 years – thus, despite 10 years experience of cART, initial treatment responses in children, adolescents and older HIV-infected individuals have been poorly documented
- As these two groups are likely to contribute significantly to the global HIV epidemic in the future, it is essential that accurate information is available on their treatment outcomes
- The aim of this analysis was to study the influence of age (from infancy to seniority) on the initial virological and immunological responses to cART, and on longer-term clinical outcomes

METHODS

The COHERE Study

- COHERE is a collaboration of 33 cohorts from 30 European countries (see Box); participating cohorts contribute data on over 246000 adults, 6410 children and 28000 infected and pregnant mothers and offspring
- Two regional coordinating centres (ISPED, Bordeaux and CHIP, Copenhagen) oversee the collection of data and quality assurance
- Each cohort submits information on a restricted dataset using the HIV Cohort Data Exchange Protocol (HICDEP), including data on patient demographics, use of cART, CD4 counts and HIV RNA measurements and clinical (AIDS and death) events

Statistical methods

- Included patients were antiretroviral-naïve when starting cART (defined as the concomitant use of three antiretroviral drugs) between 1998-2006 and had ≥1 CD4 count and viral load (VL) pre-cART and over follow-up
- Time to confirmed (2 consecutive) VL<50 copies/ml (initial virological response), confirmed CD4 increase >100 cells/mm^3 (immunological response) from pre-cART levels and a new AIDS-defining event or death were described using Kaplan-Meier plots and analysed using Cox proportional hazards regression. Children <6 years of age were excluded from these analyses due to lack of comparability of pre-cART CD4 counts between very young children and older children/adults
- Patient follow-up in the absence of an endpoint was censored on the date of the patient's last clinic visit.
- Covariates considered included age group, gender, country of origin, year of starting cART, pre-cART CD4 and VL, AIDS and initial cART regimen; a series of sensitivity analyses considered the robustness of the findings to the choice of the definitions of response

RESULTS

Characteristics of individuals in study

Of 67659 individuals starting cART, 49921 eligible individuals were included in the analyses (Table 1); other individuals were excluded due to lack of baseline CD4 count and VL (n=14629) and lack of subsequent follow-up (n=3113)

Initial cART regimens were:

- Non-ritonavir boosted PI regimen, n=14027 (28%)
- Ritonavir-boosted PI regimen, n=9705 (19%)
- NNRTI-regimen, n=18710 (38%)
- Other combinations, n=7479 (15%)

Box: Cohorts participating in COHERE Collaboration

AMACS (Greece)	HIV-MIP-Mothers & HIV-MIP-Infants (Spain)
ANRS CO1/CO10 EPF (France)	ICC (Italy)
ANRS CO2 SEROCO (France)	ICONA (Italy)
ANRS CO3 AQUITAINE (France)	IMIT (Italy)
ANRS CO4 French Hospital's Database on HIV	ITLR-Mothers & ITLR-Infants (Italy)
ANRS CO6 PRIMO (France)	KOMPNET (Germany)
ANRS CO8 COPILOTE (France)	Madrid Cohort HIV Children (Spain)
ATHENA (Netherlands)	MOCHIV-Mothers & MoCHIV-Infants (Switzerland)
CASCADE (Europe)	Modena Cohort Study (Italy)
UK CHIC (UK)	NSHPC-Mothers & NHPS-Infants (UK)
CHIPS (UK and Ireland)	PISCIS (Spain)
Co-RIS (Spain)	San Raffaele (Italy)
Danish HIV Study (Denmark)	Swiss HIV Cohort Study (SHCS, Switzerland)
ECS (Europe)	St. Pierre (Belgium)
EuroSIDA (Europe)	The Italian MASTER Cohort (Italy)
Frankfurt HIV Cohort Study (Germany)	VACH (Spain)
GEMES-Haemo (Spain)	

Table 1: Characteristics of 49,921 antiretroviral-naïve individuals included in analyses, COHERE 2006

Total number of patients		49921	(100%)
Median (IQR*) age (years):		37	(31, 43)
Female gender:		14228	(29%)
Mode of infection:	Homo/bisexual	15780	(32%)
	Injecting drug use	7541	(15%)
	Heterosexual	20233	(41%)
	Perinatal	652	(1%)
	Other	2355	(5%)
	Unknown	3360	(7%)
Country of origin:	Europe	30655	(61%)
	Africa	6774	(14%)
	Other	2785	(6%)
	Unknown	9707	(19%)
Median (IQR) pre-cART CD4 count (cells/mm^3)		210	(91, 338)
Median (IQR) pre-cART VL (log_{10} copies/ml)		4.9	(4.3, 5.4)
Previous AIDS diagnosis		12997	(26%)
Year of starting cART	1998-1999	15278	(31%)
	2000-2001	13447	(27%)
	2002-2003	12280	(25%)
	2004-2006	8916	(18%)

* IQR – inter-quartile range

Table 2: Selected characteristics of individuals in the different age groups, COHERE 2006

	Age group (years)									
	<2	2-5	6-12	13-17	18-29	30-39	40-49	50-54	55-59	≥60
Number of patients (% of total)	223 (0.5)	184 (0.4)	219 (0.4)	201 (0.4)	9134 (18.3)	22410 (44.9)	11588 (23.2)	2693 (5.4)	1656 (3.3)	1613 (3.2)
Year of starting cART (%)										
1998-1999	30	31	22	14	32	34	26	28	27	27
2000-2001	31	22	20	30	27	28	26	27	26	24
2002-2003	24	28	30	31	23	23	27	26	27	26
2004-2006	16	19	29	25	18	15	21	19	20	23
Female gender %	56	41	45	63	45	28	20	18	18	20
Mode of infection %										
Homo/bisexual	-	-	-	3	28	32	34	39	35	32
Injection drug use	-	-	-	4	11	21	16	4	1	0
Heterosexual	-	-	-	38	50	37	38	44	49	51
Perinatal	98	94	89	28	0	-	-	-	-	-
Other/unknown	2	6	11	28	11	11	12	13	15	17
Regimen type %										
Unboosted PI	32	27	19	23	31	30	24	26	24	24
Ritonavir-boosted PI	14	10	15	14	18	18	23	24	22	21
NNRTI	24	44	52	44	38	38	37	35	38	39
Other	31	19	14	18	14	15	16	16	16	16

The regimen consisted of 3, 4 or ≥5 drugs in 36693 (74%), 11971 (24%) and 1257 (2%) patients, respectively (low-dose ritonavir counted as a separate drug). The most common PIs received were ritonavir (24%), nelfinavir (19%), indinavir (14%) and lopinavir (13%); 23% and 19% of individuals received efavirenz and nevirapine, respectively.

The baseline characteristics of patients according to age are shown in Table 2 and Figure 1. Treatment regimens were broadly similar, although very young children seemed slightly more likely to receive regimens including NNRTIs or 'other' regimens. The frequency of laboratory monitoring was similar across all age groups, with a median of 4 CD4 counts in the first year of cART

Initial virological response

Overall, 53.7% of individuals achieved a confirmed VL response to cART by one year (Figure 2a); the probability of an initial virological response was lower in those aged 6-12 and 13-17 compared to those aged 30-39 years, and was higher in those aged 50-54, 55-59 and ≥60, in both unadjusted and adjusted analyses (Figure 3a)

Initial immunological response

Overall, 59.2% of individuals achieved a confirmed CD4 response by one year (Figure 2b). Compared to those aged 30-39 years, the chance of an immunological response was higher in younger individuals and was reduced in those aged ≥60 years (Figure 3b); these differences were particularly marked for the 6-12 year age group, who were 61% more likely to experience a confirmed immunological response than those aged 30-39 years. Differences between the other age groups were relatively small

Clinical outcomes

A new AIDS event or death developed in 6355 individuals (13%) following initiation of cART (Kaplan-Meier estimate of 8.1% by 1 year). Older individuals were more likely to develop such an event. Adjusted hazard ratios [95% confidence intervals] were 1.19 [1.05-1.34] and 1.34 [1.19-1.51] for those aged 55-59 years and ≥60 years, compared to those aged 30-39 years

Figure 1: Median (IQR) pre-cART CD4 counts (blue) and VL (purple) in all age groups, COHERE 2006

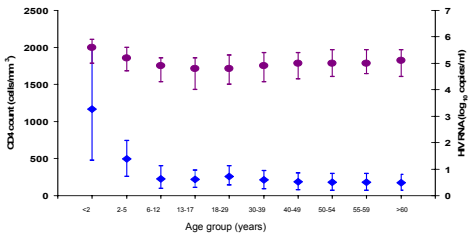
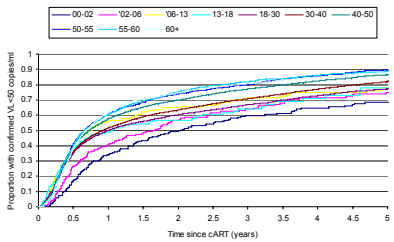


Figure 2: Kaplan-Meier plot showing time to confirmed responses in the different age groups, COHERE 2006
a) Virological response



b) Immunological response

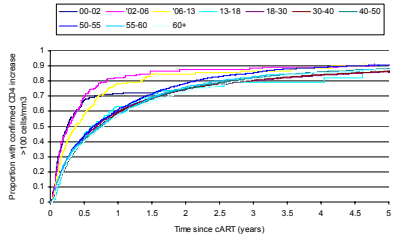
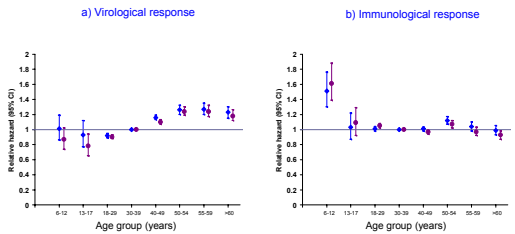


Figure 3: Unadjusted (blue) and adjusted (purple) relative hazards for confirmed a) virological and b) immunological responses in the different age groups. Estimates are adjusted for year of starting cART, pre-cART CD4 and VL, AIDS, gender, origin and initial cART regimen, COHERE 2006



SUMMARY AND CONCLUSIONS

- Despite differences in pre-cART clinical status, responses to cART were generally good at all ages. Older individuals experienced slightly better VL responses, but poorer CD4 responses, possibly due to age-related immune impairment; this poorer CD4 response appears to be associated with a poorer clinical outcome in this group.
- CD4 responses were best in young children, although the poorer VL response in these individuals may increase the risk of acquired resistance
- These findings may be helpful for clinicians initiating antiretroviral therapy among individuals of different ages; closer follow-up of virological response in younger patients and immunological response in older patients may be appropriate
- Due to problems with determining a comparable immune response in very young children, children aged <6 years were excluded from formal analyses; ongoing work aims to identify common measures of immunosuppression that can be used in all age groups, thus allowing a more formal comparison of outcomes in the very young
- Although our analyses may be biased by differences in the interpretation of CD4 counts in children/adults, and the use of different VL assays, results were generally robust to the choice of definitions used in analyses

ACKNOWLEDGEMENTS

Working group for the study of age: Caroline A Sabin (Project leader), Colette J Smith (statistician), Antonella d'Arminio Monforte (ICONA), Manuel Battegay (SHCS), Clara Gabiano (ITLR), Luisa Galli (ITLR), Sibyl Geelen (ATHENA), Diana Gibb (CHIPS), Marguerite Guiguet (FHDH), Ali Judd (CHIPS), Catherine Leport (COPILOTE), Charlotte Lewden (AQUITAINE), Nikos Pantazis (AMACS), Kholoud Porter (CASCADE), Francois Raffi (COPILOTE), Claire Thorne (ECS), Carlo Torti (Italian Master Cohort), Sarah Walker (CASCADE), Josiane Warszawski (EPF), Uwe Wintergerst (KOMPNET)

COHERE Steering Committee: *Executive Committee:* Ian Weller (Chair, University College London), Dominique Costagliola (Vice-chair, FHDH), Bruno Ledergerber (Vice-chair, SHCS), Jens Lundgren (Head, Copenhagen Regional Co-ordinating Center), Genevieve Chene (Head, Bordeaux Regional Co-ordinating Center); *Cohort representatives:* Giota Touloumi (AMACS), Josiane Warszawski (EPF), Laurence Meyer (SEROCO), François Dabis (AQUITAINE), Murielle Mary Krause (FHDH), Cecile Goujard (PRIMO), Catherine Leport (COPILOTE), Frank de Wolf (ATHENA), Peter Reiss (ATHENA), Kholoud Porter (CASCADE), Maria Dorrucci (CASCADE), Caroline Sabin (UK CHIC), Diana Gibb (CHIPS), Julia Del Amo (Co-RIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Schlomo Staszewski (Frankfurt), Santiago Perez-Hoyos (GEMES-Haemo), Jesus Almeda (HIV-MIP), Andrea Antinori (ICC), Antonella d'Arminio Monforte (ICONA, IMIT), Pier-Angelo Tovo (ITLR), Bernd Salzberger (KOMPNET), Gerd Fätkenheuer (KOMPNET), Jose Ramos (Madrid Cohort), Manuel Battegay (MoCHIV; Swiss HIV Cohort Study), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M Miro (PISCIS), Antonella Castagna (San Raffaele), Stephane de Wit (St. Pierre Cohort), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH); *European AIDS Treatment Group:* Nikos Dedes; *Project Leaders:* Caroline Sabin, Andrew Phillips, Hansjakob Furrer, Ole Kirk, Matthias Egger, François Dabis, Marie-Louise Newell, Jonathan Sterne, Amalio Telenti.

Sources of funding: Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS), Dutch HIV Monitoring Foundation, Danish Augustinus Foundation