Response to combination antiretroviral therapy: variation by age

The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group

Objective: To provide information on responses to combination antiretroviral therapy in children, adolescents and older HIV-infected persons.

Design and setting: Multicohort collaboration of 33 European cohorts.

Subjects: Forty-nine thousand nine hundred and twenty-one antiretroviral-naive individuals starting combination antiretroviral therapy from 1998 to 2006.

Outcome measures: Time from combination antiretroviral therapy initiation to HIV RNA less than 50 copies/ml (virological response), CD4 increase of more than 100 cells/μl (immunological response) and new AIDS/death were analysed using survival methods. Ten age strata were chosen: less than 2, 2–5, 6–12, 13–17, 18–29, 30–39 (reference group), 40–49, 50–54, 55–59 and 60 years or older; those aged 6 years or more were included in multivariable analyses.

Results: The four youngest age groups had 223, 184, 219 and 201 individuals and the three oldest age groups had 2693, 1656 and 1613 individuals. Precombination antiretroviral therapy CD4 cell counts were highest in young children and declined with age. By 12 months, 53.7% (95% confidence interval: 53.2–54.1%) and 59.2% (58.7–59.6%) had experienced a virological and immunological response. The probability of virological response was lower in those aged 6–12 (adjusted hazard ratio: 0.87) and 13–17 (0.78) years, but was higher in those aged 50–54 (1.24), 55–59 (1.24) and at least 60 (1.18) years. The probability of immunological response was higher in children and younger adults and reduced in those 60 years or older. Those aged 55–59 and 60 years or older had poorer clinical outcomes after adjusting for the latest CD4 cell count.

Conclusion: Better virological responses but poorer immunological responses in older individuals, together with low precombination antiretroviral therapy CD4 cell counts, may place this group at increased clinical risk. The poorer virological responses in children may increase the likelihood of emergence of resistance.

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Keywords: age, clinical outcome, combination antiretroviral therapy, HIV infection, immunological response, virological response

Introduction

Although we know much about the clinical [1,2], immunological [3] and virological [4] benefits of combination antiretroviral therapy (cART), most of this information comes from studies of adults aged from 18 to 50 years. As the HIV epidemic has evolved, an increasing proportion of those infected with HIV fall outside this age range [5,6]. The impact of age on the outcomes of cART is unclear: some studies have reported improved adherence [7,8] and better virological responses in older adults than in younger adults [9,10], whereas others have reported similar [11–14] or poorer [15,16] outcomes. Older patients may experience a poorer immune recovery on cART [7,9,10,14,17–22], although these findings have not been universal [12,13]. After initiation of cART, young children appear to have better CD4 recovery than older children [23,24]. As yet, no studies

Correspondence to Professor Caroline Sabin, Research Department of Infection and Population Health, Division of Population Health Royal Free and University College Medical School, Rowland Hill Street, London, NW3 2PF, UK.
E-mail: c.sabin@pcps.ucl.ac.uk
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have directly compared responses to cART in children and adults.

The number of children and older adults recruited to most cohorts is small, limiting any comparisons between age groups. The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study is a collaboration of observational studies across Europe, providing information on more than 250 000 HIV-positive individuals across a wide age range. The aim of this analysis was to investigate the influence of age on the immunological, virological and clinical responses to cART in this population.

Methods

The COHERE collaboration

COHERE is a collaboration of 33 observational cohort studies in 30 European countries. The collaboration was established in 2005 with the objective of conducting hypothesis-driven research on the prognosis and outcome of HIV-infected individuals across Europe. Each cohort submits information using a standardized data format [the HIV Collaboration Data Exchange Protocol (HICDEP) [25]] to co-ordinating centres at the Copenhagen HIV Program (CHIP), Copenhagen, Denmark, or the Institut de Santé Publique d'Épidémiologie et de Développement (ISPED), Bordeaux, France. Data collected include information on patient demographics, use of cART, CD4 cell counts and percentages, HIV RNA viral loads, AIDS and deaths. The co-ordinating centres ensure adherence to strict quality assurance guidelines and perform data checks, including the removal of duplicate records from patients participating in more than one cohort. Further information is given at http://www.cphiv.dk/COHERE/tabid/295/Default.aspx and http://etudes.isped.u-bordeaux2.fr/cohere/.

Patient inclusion/exclusion criteria

Previously antiretroviral-naive individuals starting cART (three or more antiretrovirals) from 1 January 1998 until 31 July 2006 (when data were merged) were considered for inclusion. Patients were excluded if their date of birth was missing or they did not have at least one CD4 cell count and viral load measurement available in both the 6 months before cART (precART values) and following the start of cART. For each individual, follow-up began on the date of starting cART and ended on the date of last recorded CD4 cell count, CD4 percentage or viral load measurement.

Statistical methods

Age at cART was fitted as a categorical variable to allow for nonlinear trends with the following age groups chosen *a priori*: less than 2, 2–5, 6–12, 13–17, 18–29, 30–39 (reference category), 40–49, 50–54, 55–59 and 60 years or older. The narrow age bands in the younger age groups allowed us to differentiate infants, toddlers, young children and adolescents in whom biological and behavioural factors may differ; among older individuals ($\geq$50 years), 5-year age groups were chosen to allow for more detailed examination of older age. The impact of age on the time to virological (the first of two consecutive viral loads $<$50 copies/ml) and immunological [the date of the first sustained (measured on two consecutive occasions) increase of at least 100 cells/μl in CD4 cell count from precART levels] responses was assessed using Kaplan–Meier methods and Cox proportional hazards models. Plots of the log[−log(survival time)] against log(time) were inspected to ensure the validity of the proportional hazards assumption. Factors adjusted for were sex, year of cART, precART CD4 cell count and viral load, precART AIDS diagnosis, ethnic origin and regimen type. Mode of infection and cohort were not included due to high colinearity with age group. Children aged less than 6 years were excluded from multivariable analyses, as the precART CD4 cell count cannot be directly compared with that of adults in this age group [26]. The frequency of viral load and CD4 cell count monitoring was comparable across age groups. An intent-to-continue treatment approach was used, as we were interested in the strategy of starting cART rather than the effect of the initial cART regimen, and thus treatment switches and discontinuations were ignored in our main analyses.

Using a similar approach, we also investigated the time to the first new AIDS event or death from any cause, the first new AIDS event, the time to discontinuation/switch of one or more antiretroviral in the regimen, and the time to complete cART discontinuation, adjusting for the factors listed previously. A further analysis also considered the proportion of patients with a CD4 cell count of more than 200 cells/μl 12 months after initiation of cART; these data were analysed using multivariable logistic regression models (patients with precART CD4 cell counts $>$200 cells/μl were included in these analyses as postcART CD4 cell counts can both decrease and increase). Finally, we used mixed effects models to describe the overall pattern of CD4 cell count in the first 5 years of cART for each age group. A piecewise linear model was used to estimate changes over time, with the slope allowed to change at 3, 6, 12, 24, 38 and 48 months following cART initiation (unstructured correlation matrix). These analyses are descriptive and not adjusted for potential confounders.

Although the majority of patients in this study had HIV RNA monitoring performed using an ultrasensitive assay with a lower limit of quantification of 50 copies/ml, the assays used to perform HIV RNA monitoring have increased in sensitivity over time. Individuals who achieved an 'undetectable' viral load measured with a less sensitive assay (usually a lower limit of quantification of 400 copies/ml) would not be judged to have reached our endpoint unless their clinic subsequently switched to a more sensitive assay at a later point in time, and thus the

time to achieve an undetectable viral load may be overestimated. Furthermore, the choice of RNA assay may vary from cohort to cohort. Thus, a number of sensitivity analyses were performed to investigate the robustness of the results to the choice of the endpoint. In particular, we changed the definition of response to use a cut-off of 400 copies/ml (to allow for measurements performed using less sensitive assays) and restricted our analyses to patients starting cART from 2001 onwards (to account for the use of less sensitive assays in earlier time periods). We also considered a virological endpoint based on only a single viral load measurement less than 50 copies/ml and changed the definition of immunological response to a single CD4 cell count of more than 100 cells/μl higher than precART levels or a 10% increase compared with precART levels. Consistent results were obtained from all sensitivity analyses. Statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

In total, 67 659 individuals starting cART from 1 January 1998 with a recorded date of birth were considered. Of these, 14 625 (22%) had no precART viral load or CD4 cell count measurement and a further 3113 (5%) had no follow-up viral load or CD4 cell count measurement, leaving 49 921 patients in our analyses. Compared with these individuals, those without a precART viral load/CD4 cell count were more likely to have started cART in earlier calendar years (38% of those excluded started cART before 2000 vs. 31% of those included), to have an AIDS diagnosis (32 vs. 26%) and to have acquired HIV through injecting drug use (26 vs. 15%). In contrast, those without follow-up, viral loads/CD4 cell counts started cART in later calendar years (47% of excluded individuals started cART in 2004–2006 vs. 18% of those included). The distribution of age was similar in both the groups.

The age of participants ranged from 4 days to 87 years (Table 1). Forty-four percent of those aged less than 2 years at the start of cART were men; this proportion rose to 80% among those aged 60 years or older. Virtually all those aged less than 12 years had acquired HIV perinatally, whereas 28% of those aged 13–17 years had acquired HIV through mother-to-child transmission and 38% through heterosexual sex. There were marked differences in the precART CD4 cell count, being highest in the youngest age groups and declining thereafter. The precART viral load was also higher in the youngest age groups, with a median value of 5.6 log copies/ml in those aged less than 2 years, falling to 4.8 log copies/ml in those aged 13–17 years, before rising again to 5.1 log copies/ml in those aged 60 years or older. Patients were followed for a median [interquartile range (IQR)] of 3.0 (1.3, 5.1) years after starting cART (81% were followed for at least a year), with no large differences between age groups.

Virological response to combination antiretroviral therapy

By 12 months after starting cART, 54% of patients had experienced a virological response with the poorest responses in those aged less than 2 and 2–5 years and the best responses in those aged 50–59, 60–64 and 60 years or older (Table 2 and Fig. 1a). These differences were confirmed in the proportional hazards model (Fig. 2a). Compared with those aged 30–39 years, those aged 6–12, 13–17 and 18–29 years when starting cART were 13% [adjusted hazard ratio 0.87, 95% confidence interval (0.74–1.02)], 22% [0.78 (0.65–0.94)], and 10% [0.90 (0.88–0.93)] less likely to experience a virological response to cART. The 40–49, 50–54, 55–59 and 60 years or older age groups all had a higher chance of experiencing a response. The chance of experiencing a good virological response was also associated with later calendar periods, lower precART CD4 cell count and viral load, unknown/non-European origin and receipt of nonnucleoside revese transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitor (2NRTI) regimens (data not shown).

Immunological response to combination antiretroviral therapy

By 12 months after starting cART, 59% of individuals had experienced an immunological response, with the greatest responses in those aged less than 2, 2–5 and 6–12 years (72, 82 and 78%, respectively). Immunological responses were lower and similar across the adult groups (Table 2 and Fig. 1b). After adjustment (Fig. 2b), those aged 6–12, 13–17 and 18–29 years were more likely to experience a response compared with those aged 30–39 years. Among older adults, immunological responses were generally similar across age groups, although those aged 60 years or older were 7% less likely to experience a response [0.93 (0.87–0.98)]. Other predictors of an improved initial immunological response were later years of starting cART, lower precART CD4 cell counts, higher precART viral load, no prior AIDS diagnosis, European origin and receipt of one proteas inhibitor (1PI) + ritonavir (RTV) + 2NRTI or 1NNRTI + 2NRTI regimens (data not shown).

There were marked differences over time in the pattern of CD4 change (Fig. 3), particularly among those aged 12 years or younger. Among very young children, mean CD4 cell counts increased rapidly in the first 6 months after starting cART but decreased thereafter, reflecting the physiological decline in CD4 cell count during early childhood. Sustained CD4 increases were seen in those aged 2–5 and 5–12 years, whereas increases were more gradual, but still maintained, in those aged at least 13 years. Age trends were similar when the proportion of individuals with a CD4 cell count of more than 200 cells/μl at

Table 1. Patient characteristics at the time of starting cART, stratified by age group ($n = 49\,921$).

	<2 years	2–5 years	6–12 years	13–17 years	18–29 years	30–39 years	40–49 years	50–54 years	55–59 years	≥60 years
Total (% of all patients)	223 (0.4)	184 (0.3)	219 (0.4)	201 (0.4)	9134 (18.3)	22410 (44.9)	11588 (23.2)	2693 (5.4)	1656 (3.3)	1613 (3.2)
Age (years) [median (IQR)]	0.4 (0.3, 0.9)	3.8 (2.9, 4.8)	8.8 (7.5, 10.6)	16.5 (15.2, 17.4)	26.9 (24.5, 28.6)	35.1 (32.7, 37.4)	43.6 (41.6, 46.3)	52.2 (51.1, 53.6)	57.1 (56.0, 58.4)	64.5 (62.1, 68.4)
Sex, male [*n* (%)]	99 (44)	108 (59)	120 (55)	75 (37)	4996 (55)	16171 (72)	9255 (80)	2223 (83)	1353 (82)	1293 (80)
Mode, [*n* (%)]										
Homo/bisexual	0 (0)	0 (0)	0 (0)	5 (3)	2590 (28)	7054 (32)	3998 (34)	1051 (39)	584 (35)	508 (32)
Injecting drug	0 (0)	0 (0)	0 (0)	8 (4)	964 (11)	4610 (21)	1840 (16)	99 (4)	13 (1)	7 (0.4)
Heterosexual	0 (0)	1 (0.5)	0 (0)	76 (38)	4579 (50)	8332 (37)	4425 (38)	1182 (44)	809 (49)	829 (51)
Perinatal	218 (98)	173 (94)	194 (89)	56 (28)	11 (0)	0 (0)	0 (0)	0 (0	0 (0)	0 (0)
Other/unknown	5 (2)	10 (5.5)	25 (11)	56 (28)	990 (11)	2414 (11)	1335 (12)	361 (13)	250 (15)	269 (17)
Origin [*n* (%)]										
Africa	51 (23)	81 (44)	125 (57)	109 (54)	2058 (23)	2764 (12)	1126 (10)	229 (9)	116 (7)	115 (7)
Europe	161 (72)	93 (51)	83 (38)	58 (29)	4557 (50)	13507 (60)	7781 (67)	1941 (72)	1243 (75)	1231 (76)
Other/unknown	11 (5)	10 (5)	11 (5)	34 (17)	2519 (28)	6139 (27)	2681 (23)	523 (19)	297 (18)	267 (17)
Year of cART [*n* (%)]										
1998, 1999	66 (30)	57 (31)	47 (22)	28 (14)	2893 (32)	7565 (34)	2983 (26)	758 (28)	447 (27)	434 (27)
2000, 2001	68 (31)	40 (22)	43 (20)	60 (30)	2480 (27)	6220 (28)	2987 (26)	725 (27)	430 (26)	394 (24)
2002, 2003	53 (24)	52 (28)	66 (30)	62 (31)	2125 (23)	5178 (23)	3176 (27)	705 (26)	450 (27)	413 (26)
2004, 2005, 2006	36 (16)	35 (19)	63 (29)	51 (25)	1636 (18)	3447 (15)	2442 (21)	505 (19)	329 (20)	372 (23)
CD4 cell count (cells/μl) [median (IQR)]	1168 (480, 1980)	496 (255, 742)	225 (98, 402)	222 (110, 340)	256 (141, 401)	210 (90, 337)	188 (78, 301)	178 (69, 295)	178 (74, 297)	173 (70, 282)
PrecART CD4% available [*n* (%)]	179 (80)	171 (93)	189 (86)	88 (44)	3286 (36)	9124 (41)	4554 (39)	1016 (38)	624 (38)	584 (36)
CD4% [median (IQR)]	25 (15, 34)	14 (8, 20)	10 (5, 16)	15 (8, 20)	17 (10, 24)	15 (8, 21)	13 (7, 19)	12 (7, 18)	12 (7, 18)	12 (7, 18)
Viral load (log copies/ml) [median (IQR)]	5.6 (5.0, 5.9)	5.2 (4.7, 5.6)	4.9 (4.3, 5.2)	4.8 (4.0, 5.2)	4.8 (4.2, 5.3)	4.9 (4.3, 5.4)	5.0 (4.4, 5.4)	5.0 (4.5, 5.5)	5.0 (4.6, 5.5)	5.1 (4.5, 5.5)
AIDS diagnosis, *n* (%)	94 (42)	50 (27)	42 (19)	54 (27)	1657 (18)	5727 (26)	3412 (29)	896 (33)	526 (32)	539 (33)
NNRTIs received [*n* (%)]										
Nevirapine	105 (47)	59 (32)	46 (21)	40 (20)	1923 (21)	4388 (20)	1953 (17)	422 (16)	284 (17)	291 (18)
Efavirenz	8 (4)	43 (23)	82 (37)	60 (30)	1925 (21)	5026 (22)	2951 (26)	656 (24)	454 (27)	416 (26)
PIs received [*n* (%)]										
Indinavir	6 (3)	3 (2)	3 (1)	9 (5)	1244 (14)	3441 (15)	1461 (13)	381 (14)	218 (13)	191 (12)
Nelfinavir	69 (31)	44 (24)	41 (19)	46 (23)	2017 (22)	4374 (20)	1908 (17)	480 (18)	272 (16)	289 (18)
Lopinavir	33 (15)	20 (11)	34 (16)	23 (11)	1026 (11)	2538 (11)	1858 (16)	427 (16)	258 (16)	241 (15)
Ritonavir	43 (19)	27 (15)	39 (18)	37 (18)	1898 (21)	4847 (22)	3193 (28)	784 (29)	454 (27)	407 (25)
NRTIs received [*n* (%)]										
Zidovudine	114 (51)	94 (51)	110 (50)	130 (65)	6034 (66)	13764 (61)	7147 (62)	1713 (64)	1072 (65)	1003 (62)
Didanosine	58 (26)	25 (14)	25 (11)	17 (9)	1482 (16)	3850 (17)	1821 (16)	423 (16)	238 (14)	243 (15)
Stavudine	81 (36)	40 (22)	46 (21)	35 (17)	2072 (23)	5745 (26)	2472 (21)	583 (22)	373 (23)	346 (22)
Lamivudine	167 (75)	157 (85)	189 (86)	184 (92)	7755 (85)	18803 (84)	9905 (86)	2313 (86)	1418 (86)	1394 (86)
Abacavir	82 (37)	78 (42)	94 (42)	43 (21)	945 (10)	2623 (12)	1533 (13)	342 (13)	190 (12)	217 (14)
Emtricabine	0 (0)	0 (0)	0 (0)	3 (2)	169 (2)	374 (2)	296 (3)	56 (2)	38 (2)	44 (3)
Tenofovir	0 (0)	1 (0)	1 (0)	14 (7)	656 (7)	1807 (8)	1277 (11)	237 (9)	135 (8)	167 (10)
Number of antiretrovirals in regimen[a] [*n* (%)]										
3	132 (59)	146 (79)	169 (77)	158 (79)	6964 (76)	16936 (76)	8073 (70)	1825 (68)	1154 (70)	1136 (70)
4	87 (39)	35 (19)	47 (22)	40 (20)	1981 (22)	4942 (22)	3180 (27)	782 (29)	441 (27)	436 (27)
≥5	4 (2)	3 (2)	3 (1)	3 (2)	189 (2)	532 (2)	335 (3)	86 (3)	61 (4)	41 (3)

(*continued overleaf*)

Table 1 (*continued*)

	<2 years	2–5 years	6–12 years	13–17 years	18–29 years	30–39 years	40–49 years	50–54 years	55–59 years	≥60 years
Regimen type [*n* (%)]										
1PI+2NRTI	71 (32)	50 (27)	42 (19)	47 (23)	2820 (31)	6760 (30)	2770 (24)	691 (26)	394 (24)	382 (24)
1PI+RTV+2NRTI	30 (14)	18 (10)	33 (15)	29 (14)	1610 (18)	3975 (18)	2663 (23)	640 (24)	363 (22)	344 (21)
1NNRTI+2NRTI	53 (24)	81 (44)	114 (52)	88 (44)	3448 (38)	8403 (38)	4333 (37)	931 (35)	636 (38)	623 (39)
Other	69 (31)	35 (19)	30 (14)	37 (18)	1256 (14)	3272 (15)	1822 (16)	431 (16)	263 (16)	264 (16)
Total follow-up (years)										
Median (IQR)	3.7 (1.8, 5.7)	3.4 (1.6, 6.0)	2.4 (1.3, 4.9)	2.2 (1.0, 3.7)	3.0 (1.3, 5.1)	3.2 (1.4, 5.3)	2.8 (1.2, 4.9)	3.1 (1.4, 5.1)	3.0 (1.4, 5.0)	2.7 (1.1, 4.8)
n (%) >1 year	191 (85.7)	156 (84.8)	173 (79.0)	148 (73.6)	7306 (80.0)	18446 (82.3)	9152 (79.0)	2183 (81.1)	1336 (80.7)	1252 (77.6)

IQR, inter-quartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
[a]Ritonavir used at a low dose to pharmacologically boost other drugs in the regimens is counted as one antiretroviral drug.

12 months was considered, with the percentage achieving this level decreasing with increased age.

Occurrence of new AIDS events, death and treatment discontinuation

The proportion of patients who experienced a new AIDS event or death by 12 months is shown in Table 2. In a multivariable model, comparable outcomes were seen across the age groups, with the exception of those aged 55–59 [1.19 (1.05–1.34)] and 60 years or older [1.34 (1.19–1.51)] years, who had poorer outcomes than those aged 30–39 years. After adjusting for the latest CD4 cell count as a time-updated covariate, the risk of AIDS remained higher in those aged 55–59 and 60 years or older [55–59 years: 1.18 (1.05–1.34); 60 years or older 1.32 (1.17–1.48)]. Similar trends by age were found when considering the time to the first new AIDS event only.

Changing or discontinuing one or more antiretroviral drug in the cART regimen in the first 12 months of cART was common (Table 2). In multivariable analysis, those aged 6–12 years were 40% less likely to switch or discontinue any antiretroviral drug compared with those aged 30–39 years [0.60 (0.50–0.72)]; in contrast, those aged 18–29 and 60 years or older were more likely to make a treatment switch [1.06 (1.03–1.09) and 1.07 (1.01–1.14), respectively]. However, complete treatment discontinuation for at least 2 weeks was rare (Table 2). Compared with those aged 30–39 years when starting cART, higher treatment discontinuation rates were observed among those aged 13–17 years [1.31 (0.99–1.73)] and 18–29 years [1.11 (1.06–1.17)], whereas lower discontinuation rates were observed among those aged 6–12 [0.81 (0.59–1.12)], 40–49 [0.83 (0.79–0.87)], 50–54 [0.71 (0.46–0.78)], 55–59 [0.74 (0.66–0.83)] and 60 years or older [0.73 (0.64–0.82)] years.

Discussion

To our knowledge, this study reflects the first attempt to describe responses to cART across such a wide age span and with such a large sample size. This has enabled us to consider narrow age groups among children, adolescents and older patients to investigate in detail whether differences exist in the response to cART among these groups. Although responses to cART were reasonable across all age groups, age was a predictor of many of the outcomes considered, even after controlling for precART disease stage and other known confounders. These findings are of clinical importance, as they may permit treatment guidelines (particularly relating to the timing of initiation of HAART and frequency of subsequent patient monitoring) to be targeted to specific age groups. Furthermore, accurate information on the expected outcomes in each age group will allow clinicians to judge whether their own patients are responding better or worse than would be expected for someone of a particular age.

Table 2. Percentage (95% confidence interval) who had experienced an event by 12 months after initiation of combination antiretroviral therapy.

Age group	Virological response	Immunological response	CD4 cell count at 12 months >200 cells/μl[a]	New AIDS event/death	New AIDS event	Discontinuation or switch of at least one antiretroviral	Discontinuation of all antiretrovirals
<2	34.0 (27.6, 40.5)	71.8 (65.7, 77.9)	99.4 (96.7, 100.0)	12.4 (8.0, 16.8)	11.5 (7.3, 15.8)	34.2 (27.9, 40.6)	7.9 (4.2, 11.5)
2–5	40.2 (32.7, 47.6)	82.2 (75.6, 87.5)	97.7 (93.5, 99.5)	7.4 (3.5, 11.3)	7.4 (3.5, 11.3)	26.0 (19.5, 32.5)	6.2 (2.7, 9.8)
6–12	56.3 (49.2, 63.4)	78.0 (72.0, 84.0)	92.0 (86.4, 95.8)	7.4 (3.8, 11.1)	6.5 (3.0, 9.9)	27.4 (21.3, 33.6)	6.7 (3.2, 10.3)
13–17	45.6 (41.2, 55.9)	63.2 (55.9, 70.6)	85.6 (79.6, 91.6)	4.8 (1.7, 7.8)	4.8 (1.7, 7.8)	49.7 (42.4, 56.9)	15.3 (10.0, 20.5)
18–29	50.0 (48.9, 51.1)	59.8 (58.7, 60.9)	86.7 (85.9, 87.6)	5.4 (4.9, 5.9)	5.2 (4.7, 5.6)	48.9 (47.8, 49.9)	14.8 (14.1, 15.6)
30–39	51.6 (51.0, 52.3)	59.0 (58.4, 59.7)	80.5 (79.9, 81.1)	7.6 (7.2, 7.9)	7.0 (6.6, 7.3)	45.9 (45.2, 46.6)	11.4 (11.0, 11.8)
40–49	57.5 (56.5, 58.4)	57.8 (56.9, 58.8)	76.3 (75.4, 77.2)	9.4 (8.9, 10.0)	8.5 (7.9, 9.0)	47.0 (46.0, 47.9)	9.2 (8.7, 9.8)
50–54	61.4 (59.4, 63.3)	61.2 (59.3, 63.2)	75.2 (73.3, 77.1)	11.1 (9.9, 12.3)	9.6 (8.5, 10.7)	48.3 (46.3, 50.3)	6.9 (5.9, 7.9)
55–59	60.3 (57.8, 62.8)	57.9 (55.4, 60.4)	73.9 (71.4, 76.3)	10.9 (9.4, 12.5)	9.3 (7.8, 10.7)	49.0 (46.4, 51.5)	7.9 (6.5, 9.2)
≥60	61.8 (59.2, 64.4)	57.4 (54.8, 60.0)	74.7 (72.1, 77.2)	11.7 (10.1, 13.3)	9.7 (8.2, 11.2)	51.1 (48.5, 53.6)	7.3 (5.9, 8.6)
Total	53.7 (53.2, 54.1)	59.2 (58.7, 59.6)	80.1 (79.7, 80.5)	8.1 (7.8, 8.3)	7.3 (7.1, 7.5)	46.9 (46.4, 47.3)	11.0 (10.7, 11.3)
P value[b]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

All percentages are Kaplan–Meier estimates. Virological response: first of two consecutive viral loads less than 50 copies/ml. Immunological response: first of two consecutive CD4 cell counts more than 100 cells/μl higher than precART levels.
[a]Calculated based on number with CD4 more than 200 cells/μl at 12 months divided by number with a CD4 measurement at 12 months (window 4–8 months). *P* value obtained from χ^2-test.
[b]From log rank test; note that unadjusted comparisons of immunological responses are complicated by the natural decline in CD4 cells in very young children.

Despite having more advanced disease at treatment initiation (possibly due to later presentation for HIV care [27]), older people were more likely to demonstrate a good initial virological response to cART. Concerns about a greater potential for drug–drug interactions in older people, who may be receiving other concomitant medications, do not seem to lead to impaired virological responses. However, in line with previous studies [7,9,10,14,17–22], we observed a similar or slightly worse immune response among older individuals. These poorer responses, coupled with lower precART CD4 cell counts, suggest that older individuals are at greater risk of experiencing clinical events, a hypothesis that was confirmed in our study. Although it could be argued that our definition of an immunological response is likely to provide a relatively crude differentiation between those who have a good or poor response, more detailed measures of immune response were not available for most patients in this cohort. The fact that the increased risk of clinical events remained after adjustment for the latest CD4 cell count suggests that the functional impairment to the immune systems of older individuals may be more profound than expected, based on measurement of CD4 cell counts alone [28]. Clinical events may not be limited to those traditionally considered to be associated with HIV, but may include a range of additional morbidities, many of which are associated with lower CD4 cell counts [29–31] and may occur more frequently in older individuals.

After adjustment for potential confounders, children aged at least 6 years, adolescents and young adults were less likely to experience a virological response than older individuals, possibly reflecting the more disordered lifestyles that may be present among adolescents and younger adults, which, in turn, may have an impact on adherence [32]. Impaired virological responses may lead to the emergence of drug-resistant virus, the consequences of which are particularly important for children and adolescents who will need to receive antiretroviral therapy for life and in whom preservation of treatment options is essential. Interestingly, we observed an improved CD4 response in children aged 6–12 years compared with adolescents and adults, despite the poorer virological responses in this group [23]. The fact that older children and adolescents had poorer virological response but improved immunological response highlights the complex interplay between host (particularly thymic output) and virus.

We also found that children aged less than 6 years had a poorer initial virological response to treatment. Although this could be explained to some extent by the high precART viral loads in these children, formulation pharmacokinetics [33], the limited choice of antiretrovirals available for children over the study period, and adherence [34] may also play a role. Unfortunately, we were unable to include children aged less than 6 years in multivariable analyses; whereas CD4 cell counts in uninfected children fall towards adult values by mid-childhood [35–37] and have a similar prognostic value for short-term disease progression to adults from the age of 4 years [38], the high CD4 cell counts seen at birth mean that adjustment for the precART CD4 cell count may not adequately control for baseline immunological status among very young children. Although the CD4 percentage may be less variable than the CD4 cell count, the CD4 percentage may not always be recorded among adults. Further methodological studies are underway to identify appropriate statistical methods that can permit the inclusion of young children in the analyses while adjusting fully for baseline immunological status.

Infants initially had a rapid CD4 increase, although this diminished with time due to the natural decline in CD4

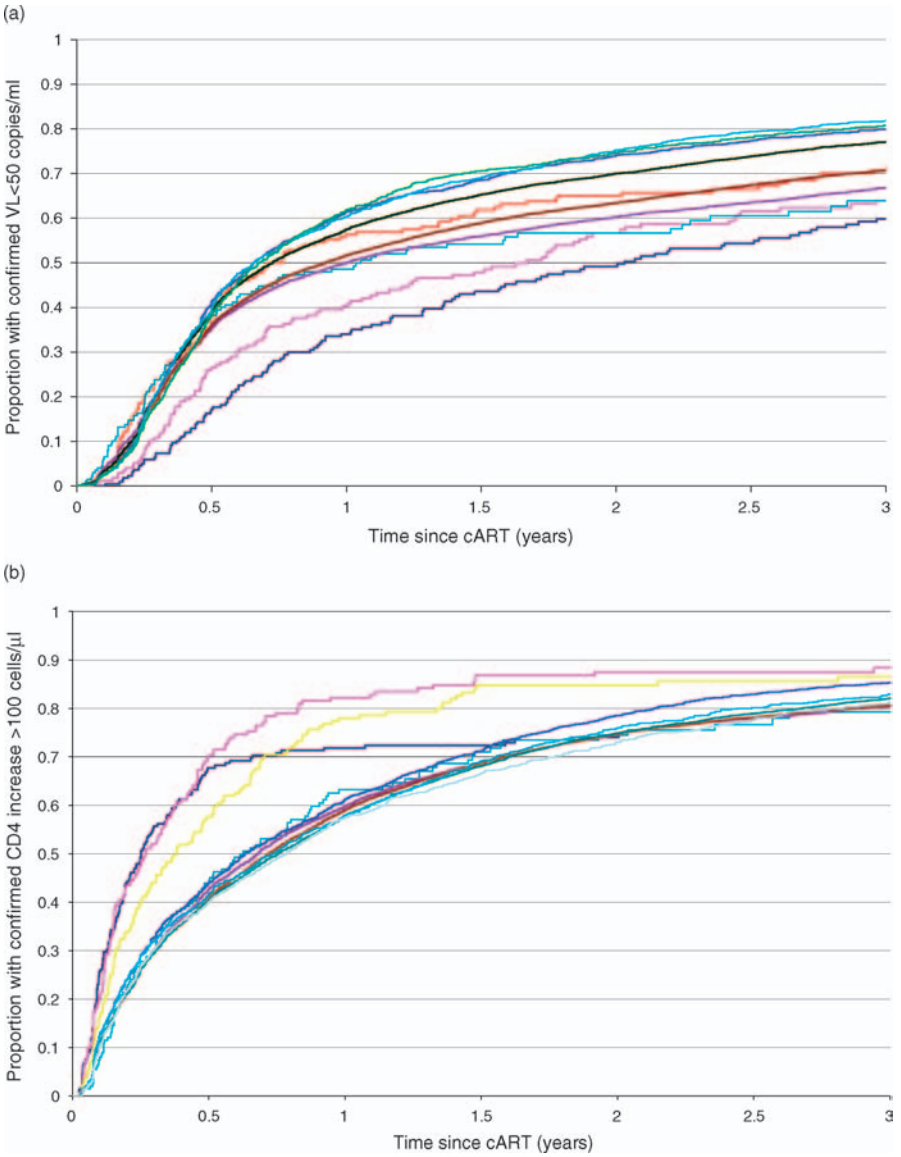

Fig. 1. Kaplan–Meier plot showing time to (a) first confirmed virological response and (b) first confirmed immunological response, stratified by age group. (a) Number of patients in each age group is as follows: (—) <2 years: 223, 128, 89, 63; (—) 2–5 years: 184, 94, 63, 44; (—) 6–12 years: 219, 75, 51, 40; (—) 13–17 years: 201, 75, 47, 27; (—) 18–29 years: 9134, 3666, 2434, 1644; (—) 30–39 years: 22 410, 8929, 5667, 3791; (—) 40–49 years: 11 588, 3882, 2223, 1399; (—) 50–54 years: 2693, 831, 465, 305; (—) 55–59 years: 1656, 530, 286, 175; (—) >60 years: 1613, 477, 246, 159. (b) Number of patients in each age group is as follows: (—) <2 years: 223, 52, 44, 38; (—) 2–5 years: 184, 28, 16, 13; (—) 6–12 years: 219, 36, 18, 13; (—) 13–17 years: 201, 51, 25, 11; (—) 18–29 years: 9134, 2882, 1429, 840; (—) 30–39 years: 22 410, 7408, 3593, 2129; (—) 40–49 years: 11 588, 3782, 1700, 923; (—) 50–54 years: 2693, 832, 361, 192; (—) 55–59 years: 1656, 547, 248, 136; (—) >60 years: 1613, 529, 250, 130.

cell counts seen in young uninfected children. The risk of a new AIDS event or death after cART was high among these very young children, in contrast to their good immune response, highlighting the high mortality in infants infected when their immune system is immature [39]. A relatively high proportion of children less than 2 years had an AIDS event before starting cART – these young children are likely to be 'fast progressers' and may appear to have a higher rate of clinical progression after starting cART than older children or adults.

Changes in cART regimen were commonly observed, particularly in adults. Treatment changes were less frequent in children, probably reflecting better tolerance of treatment and/or more limited drug options in this group. However, complete treatment discontinuation was rare at any age, although adolescents had twice the discontinuation rate of younger children and adults. The identification of ways in which therapy can be safely simplified and the development of specific interventions to improve adherence among

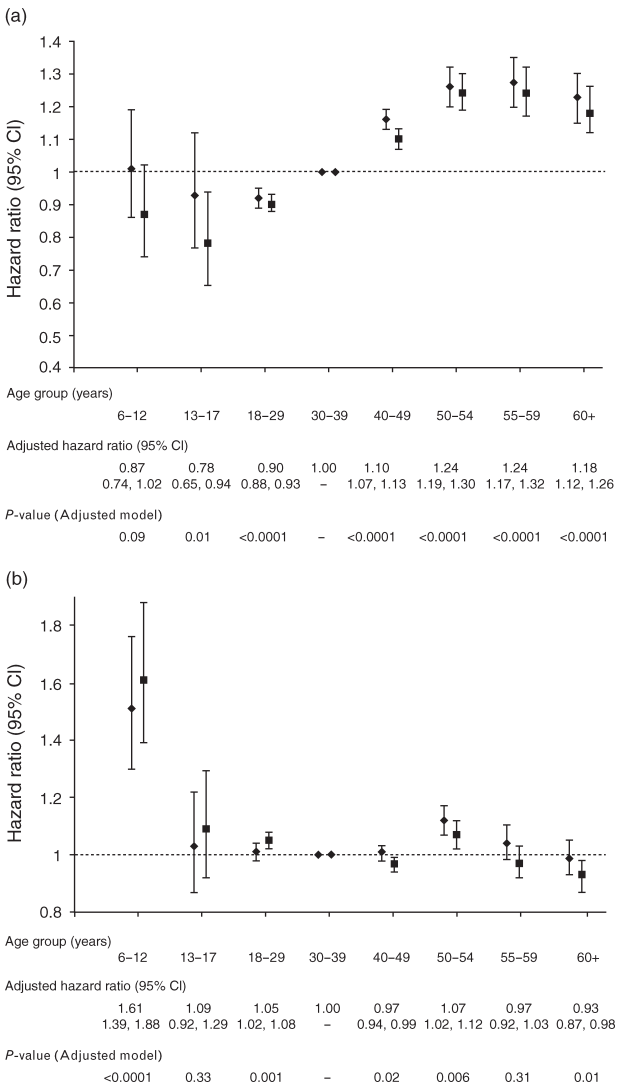

Fig. 2. Unadjusted and adjusted hazard ratios of the impact of age on time to (a) confirmed virological response and (b) confirmed immunological response. Disregarding treatment changes and discontinuations. Unadjusted hazard ratio shown with diamond and adjusted hazard ratio shown with square. Estimates from Cox proportional hazards model; multivariable hazard ratios adjusted for sex, year of starting cART, precART CD4 cell count, precART viral load, AIDS diagnosis at the time of starting cART, ethnic origin and regimen type. (a) Age group (years): 6–12, 13–17, 18–29, 30–39, 40–49, 50–54, 55–59, >60.

adolescents may help minimize the emergence of resistance in this group.

Any comparisons of treatment outcomes by age are likely to be confounded by differences in sex and ethnicity [40,41]. Our associations between age and response to cART were independent of these factors. We found no evidence of any strong associations between sex and response to treatment, although those of non-European/unknown origin had better virological but poorer immunological responses to cART. The reasons for this are unknown, but geographical origin will capture a number of factors including HIV subtype, socioeconomic status and adherence. Unfortunately, we cannot comment on the role of any behavioural differences between individuals of different ages. Owing to the high colinearity with age group, we could not adjust for route of exposure to HIV. However, when the analyses were repeated after excluding homo/bisexual men and injection drug users (so removing some of the confounding effect of this factor), the results were unchanged.

Despite its large size and broad geographical representation, a number of limitations of our observational study must be acknowledged. Although every attempt has been made to adjust for known potential confounders, we cannot rule out the presence of unknown confounders and could not adjust for hepatitis B virus and hepatitis C virus status. We were not able to consider the development of toxicities, which may also differ by age group; information on toxicities has only recently begun to be collected by cohorts and has yet to be standardized, limiting any analyses that could be performed. Furthermore, as data are collected from a large number of participating cohorts, there is the potential for data collection methods to vary from cohort to cohort. However, the rigorous data quality assurance checks and the use of a unified data collection procedure should minimize any bias that might arise from this. Although we used a stringent definition of virological response requiring the use of an ultrasensitive assay, our results were robust to the choice of this endpoint. Owing to of our exclusion criteria, patients with missing precART CD4 cell counts and/or viral loads were excluded from this analysis; as many of these patients started cART in earlier calendar periods, we felt it was appropriate to exclude these patients so that the included patients were more representative of those currently starting cART. However, alternative methods (e.g. multiple imputation) could have been used which would have permitted the inclusion of these individuals in our analyses. Finally, we cannot rule out the possibility of a healthy survivor effect, particularly among the vertically infected children, as those who start cART at at least 6 years of age must have survived to this age in order to receive treatment at this time.

In summary, although we observed reasonable responses to cART across all age groups, virological responses were better in older individuals. However, immunological responses were poorer in this group, which, in combination with low precART values, may put this group at increased risk of HIV disease progression and other clinical events. Immunological responses were best in young children, although the extent to which this increased CD4 change translates into prolonged clinical benefit is less clear. Additionally, the possibility of a poorer virological response in young children may increase the risk of acquiring resistance mutations in this group.

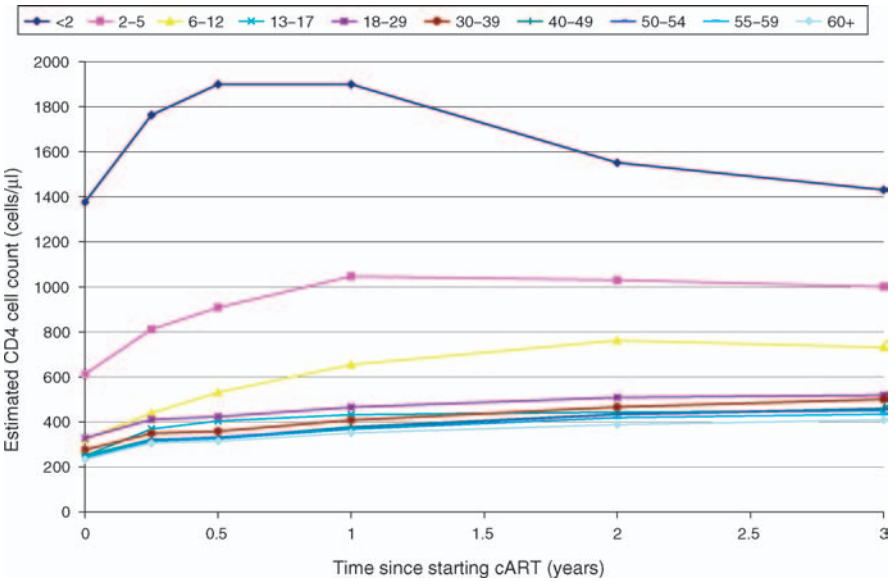

Fig. 3. Estimated change in CD4 cell count during first 3 years of cART according to age group. Number of patients in each age group is as follows: (—●—) <2 years: 223, 191, 165, 133; (—) 2–5 years: 184, 156, 129, 101; (—■—) 6–12 years: 219, 173, 129, 94; (—▲—) 13–17 years: 201, 148, 107, 75; (—✕—) 18–29 years: 9134, 7306, 5807, 4517; (—■—) 30–39 years: 22 410, 18 446, 14 876, 11 861; (—●—) 40–49 years: 11 588, 9152, 7135, 5490; (—+—) 50–54 years: 2693, 2183, 1733, 1363; (—) 55–59 years: 1656, 1336, 1062, 817; (—) >60 years: 1613, 1252, 961, 744.

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Writing 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), François Dabis (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), Genevieve Chene (Head, Bordeaux Regional Co-ordinating Center), Jens Lundgren (Head, Copenhagen Regional Co-ordinating Center).

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 (ANRS CO1 EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Cecile Goujard (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 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 Fatkenheuer (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.

All members of the writing group participated in discussions on the design of the study, the choice of statistical analyses and interpretation of the findings, and were involved in the preparation and review of the final manuscript for submission. In addition, Colette Smith and Caroline Sabin are responsible for performing all analyses; Colette Smith acts as guarantor for the analyses and has full access to the dataset.

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