

Response to Combination Antiretroviral Therapy (cART): Variation by Age

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

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Statement of authors' contributions

All members of the writing group participated in discussions about 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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Abstract

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

Design, Setting: Multi-cohort collaboration of 33 European cohorts

Subjects: 49,921 antiretroviral-naïve individuals starting cART from 1998-2006

Outcome measures: Time from cART initiation to HIV RNA <50 copies/ml (virological response), CD4 increase of >100 cells/mm³ (immunological response) and new AIDS/death were analysed using survival methods. Ten age strata were chosen: <2, 2-5, 6-12, 13-17, 18-29, 30-39 (reference group), 40-49, 50-54, 55-59 and ≥60 years; those aged ≥6 years were included in multivariable analyses.

Results: 223, 184, 219 and 201 were in the 4 youngest and 2693, 1656 and 1613 in the 3 oldest age groups. Pre-cART CD4 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 ≥60 (1.18) years. The probability of immunological response was higher in children and younger adults and reduced in those ≥60 years. Those aged 55-59 and ≥60 years had poorer clinical outcomes after adjusting for the latest CD4 count.

Conclusions: Better virological responses but poorer immunological responses in older individuals, together with low pre-cART CD4 counts, may place this group at increased clinical risk. The poorer virological responses in children may increase the likelihood of emergence of resistance.

Key words: Combination antiretroviral therapy; age; HIV infection; immunological response; virological response, clinical outcome

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 18-50 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 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 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 >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 between 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 standardised 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 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-naïve individuals starting cART (three or more antiretrovirals) from 1st January 1998 until 31st 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 count and viral load measurement available in both the 6 months before cART (pre-cART 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 count, CD4 percentage or viral load measurement.

Statistical methods

Age at cART was fitted as a categorical variable to allow for non-linear trends with the following age groups chosen *a priori*: <2, 2-5, 6-12, 13-17, 18-29, 30-39 (reference category), 40-49, 50-54, 55-59 and ≥60 years. 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 (≥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 in CD4 of at least 100 cells/mm³ from pre-cART levels) response were 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 gender, year of cART, pre-cART CD4 count and viral load, pre-cART AIDS diagnosis, ethnic origin and regimen type. Mode of infection and cohort were not included due to high co-linearity with age group. Children aged <6 years were excluded from multivariable analyses as the pre-cART CD4 count cannot be directly compared with adults in this age group [26]. The frequency of viral load and CD4 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 i) the first new AIDS event or death from any cause, ii) the first new AIDS event, iii) the time to discontinuation/switch of one or more antiretroviral in the regimen and iv) the time to complete cART discontinuation, adjusting for the factors listed previously. A further analysis also considered the proportion of patients with a CD4 count >200 cells/mm³ 12 months after initiation of cART; these data were analysed using multivariable logistic regression models (patients with pre-cART CD4 counts >200 cells/mm³ were included in these analyses as post-cART CD4 counts can decrease as well as increase). Finally, we used mixed effects models to describe the overall pattern of CD4 count in the first five 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 over-estimated. 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 <50 copies/ml, and changed the definition of immunological response to a single CD4 count >100

cells/mm³ higher than pre-cART levels or a 10% increase compared to pre-cART levels. Consistent results were obtained from all sensitivity analyses. Statistical analyses were performed using SAS version 9.1.

Results

Patient characteristics

In total, 67659 individuals starting cART from 1st January 1998 with a recorded date of birth were considered. Of these, 14625 (22%) had no pre-cART viral load or CD4 count measurement and a further 3113 (5%) had no follow-up viral load or CD4 count measurement, leaving 49921 patients in our analyses. Compared to these individuals, those without a pre-cART viral load/CD4 count started cART in earlier calendar years (38% of those excluded started cART before 2000 vs. 31% of those included), have an AIDS diagnosis (32% vs. 26%) and were more likely to have acquired HIV via injecting drug use (26% vs. 15%). In contrast, those without follow-up viral loads/CD4 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 groups.

The age of participants ranged from 4 days to 87 years (Table 1). Forty-four percent of those aged <2 years at the start of cART were male; this proportion rose to 80% amongst those aged ≥60 years. Virtually all those aged ≤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 pre-cART CD4 count, being highest in the youngest age groups and declining thereafter. The pre-cART viral load was also higher in the youngest age groups, with a median value of 5.6 log copies/ml in those aged <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. Patients were followed for a median (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 cART

By 12 months after starting cART, 54% of patients had experienced a virological response with the poorest responses in those aged <2 and 2-5 years, and the best responses in those aged 50-59, 60-64 and ≥60 years (Table 2 and Figure 1a). These differences were confirmed in the proportional hazards model (Figure 2a). Compared to 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, respectively, to experience a virological response to cART. The 40-49, 50-54, 55-59 and ≥60 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 pre-cART CD4 count and viral load, unknown/non-European origin, and receipt of NNRTI+2NRTI regimens (data not shown).

Immunological response to cART

By 12 months after starting cART, 59% of individuals had experienced an immunological response, with the greatest responses in those aged <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 Figure 1b). After adjustment (Figure 2b), those aged 6-12, 13-17 and 18-29 years were more likely to experience a response compared to those aged 30-39 years. Among older adults, immunological responses were generally similar across age groups, although those aged ≥ 60 years 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 pre-cART CD4 counts, higher pre-cART viral load, no prior AIDS diagnosis, European origin, and receipt of 1PI+RTV+2NRTI or 1NNRTI+2NRTI regimens (data not shown).

There were marked differences over time in the pattern of CD4 change (Figure 3), particularly amongst those aged ≤ 12 years. Among very young children, mean CD4 counts increased rapidly in the first 6 months after starting cART but decreased thereafter, reflecting the physiological decline in CD4 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 ≥ 13 years. Age trends were similar when the proportion with a CD4 count > 200 cells/mm³ at 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 (1.34 [1.19-1.51]) years, who had poorer outcomes than those aged 30-39 years. After adjusting for the latest CD4 count as a time-updated covariate, the risk of AIDS remained higher in those aged 55-59 and ≥ 60 years (55-59 years: 1.18 [1.05-1.34]; ≥ 60 years 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 to those aged 30-39 years (0.60 [0.50-0.72]); in contrast those aged 18-29 and ≥ 60 years 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 two weeks was rare (Table 2). Compared to those aged 30-39 years when starting cART, higher treatment discontinuation rates were observed amongst

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 (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 amongst children, adolescents and older patients to investigate in detail whether differences exist in the response to cART amongst these groups. Whilst responses to cART were reasonable across all age groups, age was a predictor of many of the outcomes considered, even after controlling for pre-cART 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.

Despite having more advanced disease 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, we observed a similar or slightly worse immune response amongst older individuals in line with previous studies [7,9,10,14,17-22]. These poorer responses, coupled with lower pre-cART CD4 counts, suggest that older individuals are at greater risk of experiencing clinical events, a hypothesis that was confirmed in our study. Whilst 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 count suggests that the functional impairment to the immune systems of older individuals may be more profound than expected, based on measurement of CD4 counts alone [28]. Clinical events may not be limited to those traditional considered to be HIV-associated, but may include a range of additional morbidities, many of which are associated with lower CD4 counts [29-31] and may occur more frequently in older individuals.

After adjustment for potential confounders, children aged ≥ 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 amongst adolescents and younger adults which may, in turn, 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 <6 years had a poorer initial virological response to treatment. Whilst this could be explained to some extent by the high pre-cART 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 <6 years in multivariable analyses; whilst CD4 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 counts seen at birth mean that adjustment for the pre-cART CD4 count may not adequately control for baseline immunological status among very young children. Whilst the CD4 percentage may be less variable than the CD4 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 whilst 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 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 <2 years had an AIDS event before starting cART - these young children are likely to be 'fast progressors' 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 amongst adolescents may help to minimise 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 gender 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, socio-economic status and adherence. Unfortunately, we cannot comment on the role of any behavioural differences between individuals of different ages. Due to the high co-linearity 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 representativeness, a number of limitations of our observational study must be acknowledged. Whilst 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 standardised, 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 minimise any bias that might arise from this. Whilst 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. Because of our exclusion criteria, patients with missing pre-cART CD4 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 amongst the vertically infected children, as those who start cART at 6 years or older must have survived to this age in order to receive treatment at this time.

In summary, whilst 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 pre-cART 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.

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Conflict of interest statement

No member of the Writing Group for this report has any financial or personal relationships with people or organizations that could inappropriately influence this work, although most members of the group have, at some stage in the past, received funding from a variety of pharmaceutical companies for research, travel grants, speaking engagements or consultancy fees.

Appendix – The COHERE Study Group

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Table 1 – Patient characteristics at the time of starting cART, stratified by age group (n=49921)

		<2	2 to 5	6 to 12	13 to 17	18 to 29	30 to 39	40 to 49	50 to 54	55 to 59	≥60
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)
Gender, n (%)	Male	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 (0.1)	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 count (cells/mm³)	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)
Pre-cART 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 (51.1)	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)
	Emtricitabine	0 (0)	0 (0)	0 (0)	3 (2)	169 (2)	374 (2)	296 (3)	56 (2)	38 (2)	44 (3)
	Tenofovir	0 (0)	1 (0.5)	1 (0.5)	14 (7)	656 (7)	1807 (8)	1277 (11)	237 (9)	135 (8)	167 (10)
Number of antiretrovirals in regimen*, 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)
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)

*ritonavir used at a low dose to pharmacologically boost other drugs in the regimens is counted as one antiretroviral drug

IQR=inter-quartile range; PI=protease inhibitor; NNRTI=non nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor.

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 count at 12 months >200 cells/mm ³ #	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*	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

All percentages are Kaplan Meier estimates

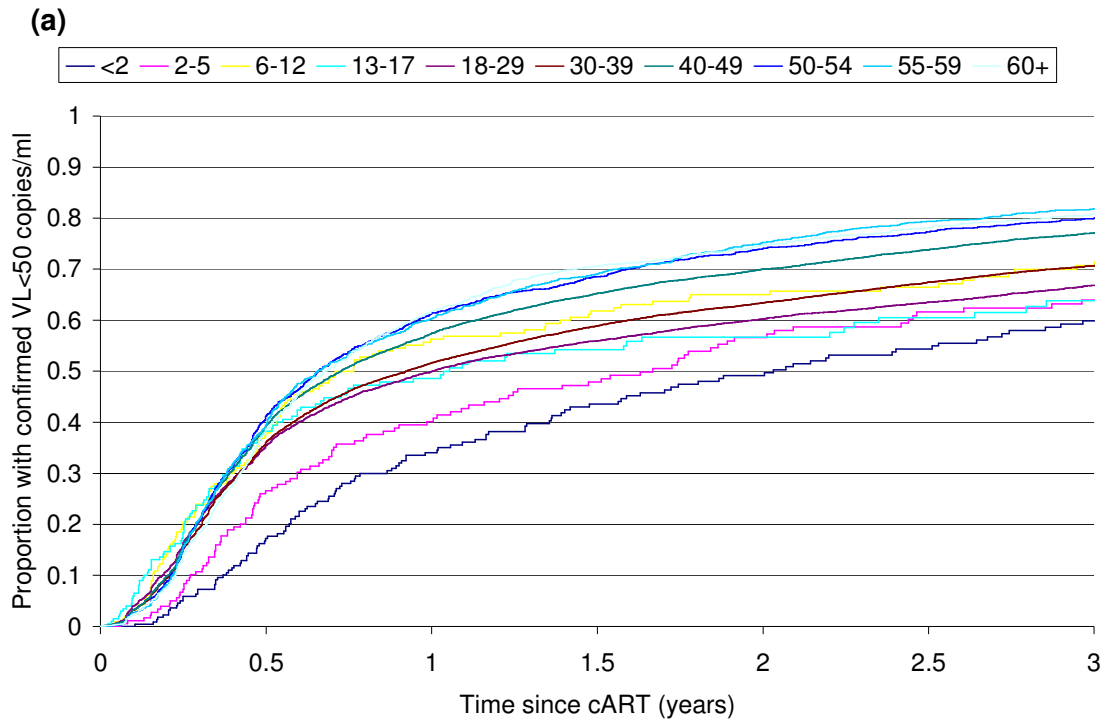
Virological response: first of two consecutive viral loads <50 copies/ml

Immunological response: first of two consecutive CD4 counts more than 100 cells/mm³ higher than pre-cART levels

calculated based on number with CD4>200 cells/mm³ at 12 months divided by number with a CD4 measurement at 12 months (window 4-8 months); p-value obtained from Chi-squared test

*from log rank test; note that unadjusted comparisons of immunological responses are complicated by the natural decline in CD4 cells in very young children

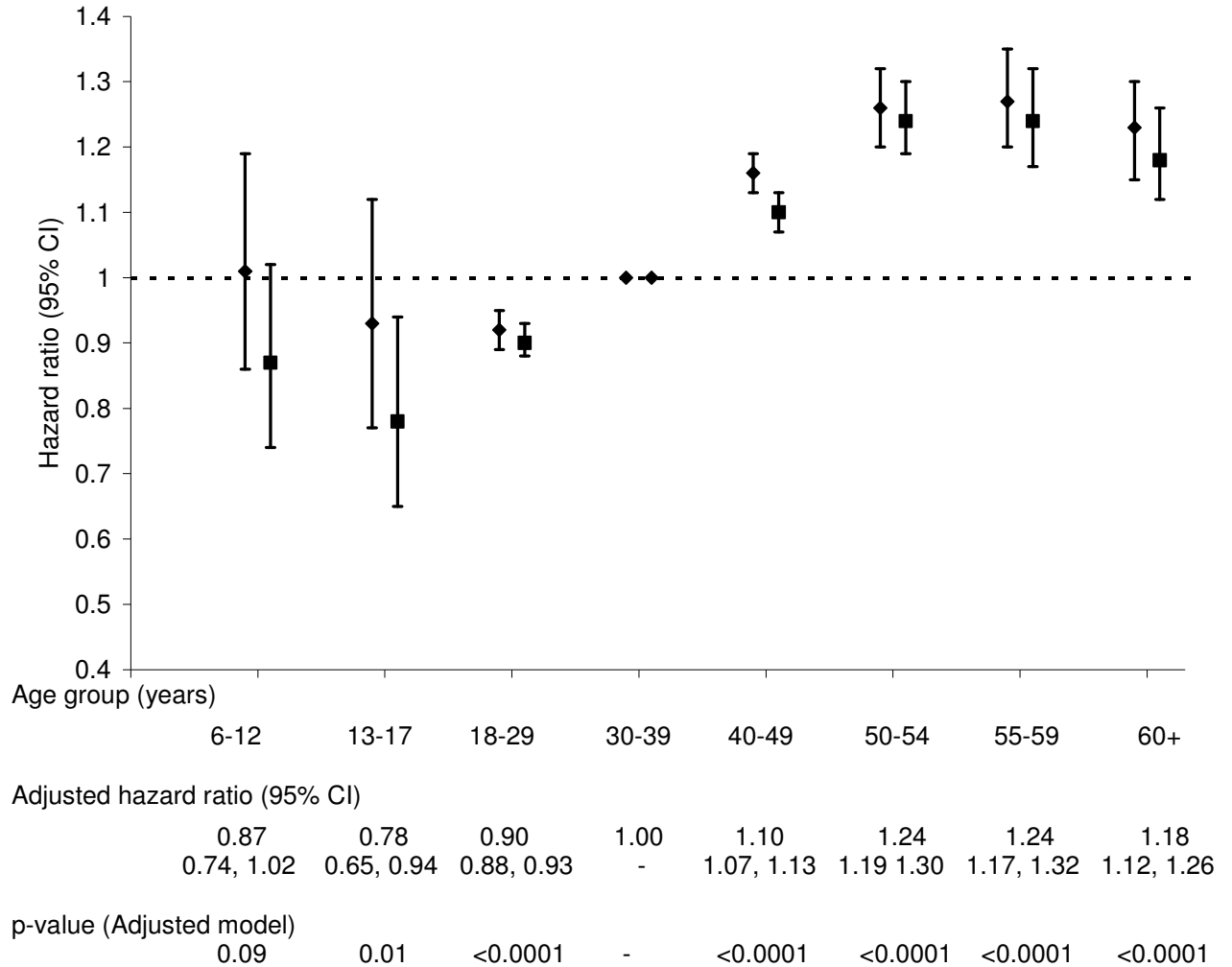
Figure 1- Kaplan-Meier plot showing time to a) first confirmed virological response, and b) first confirmed immunological response, stratified by age group



n	<2	2-5	6-12	13-17	18-29	30-39	40-49	50-54	55-59	60+
<2	223				128			89		63
2-5	184				94			63		44
6-12	219				75			51		40
13-17	201				75			47		27
18-29	9134				3666			2434		1644
30-39	22410				8929			5667		3791
40-49	11588				3882			2223		1399
50-54	2693				831			465		305
55-59	1656				530			286		175
≥60	1613				477			246		159

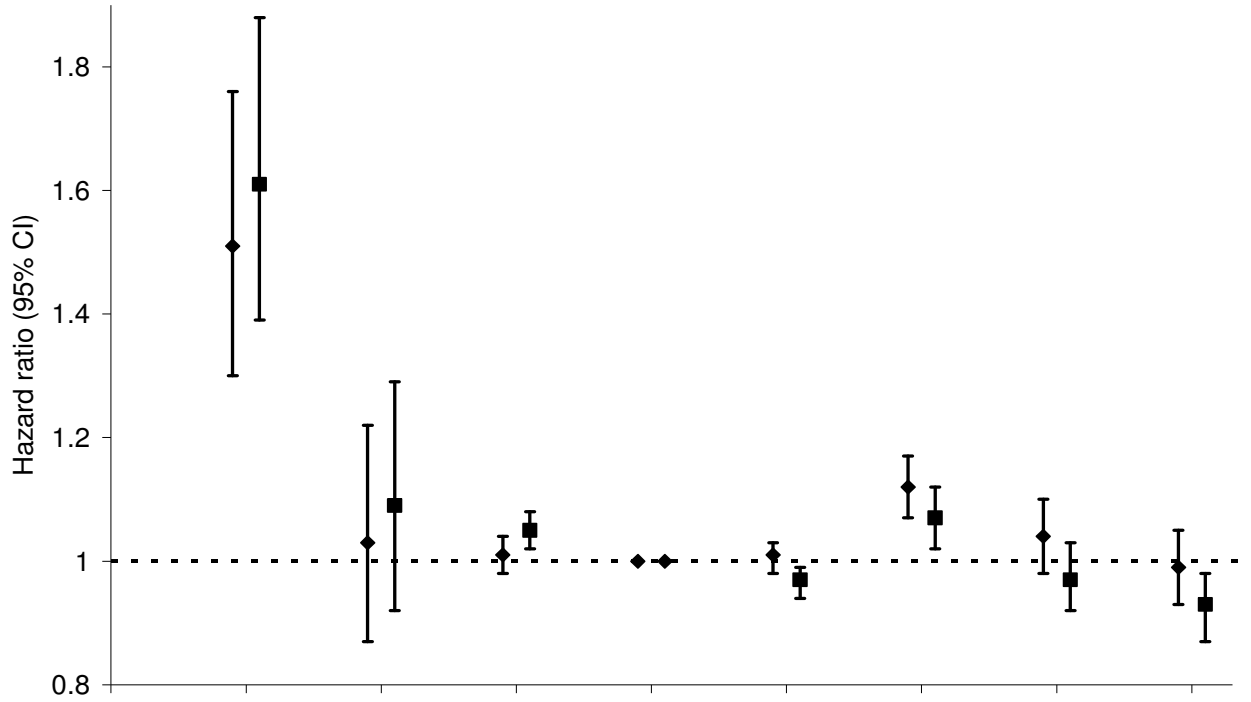
Figure 2- Unadjusted and adjusted hazard ratios of the impact of age on time to a) confirmed virological response, and b) confirmed immunological response

a)



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 gender, year of starting cART, pre-cART CD4 count, pre-cART viral load, AIDS diagnosis at the time of starting cART, ethnic origin and regimen type

b)



Age group (years)

6-12 13-17 18-29 30-39 40-49 50-54 55-59 60+

Adjusted hazard ratio (95% CI)

1.61 1.09 1.05 1.00 0.97 1.07 0.97 0.93
 1.39, 1.88 0.92, 1.29 1.02, 1.08 - 0.94, 0.99 1.02, 1.12 0.92, 1.03 0.87, 0.98

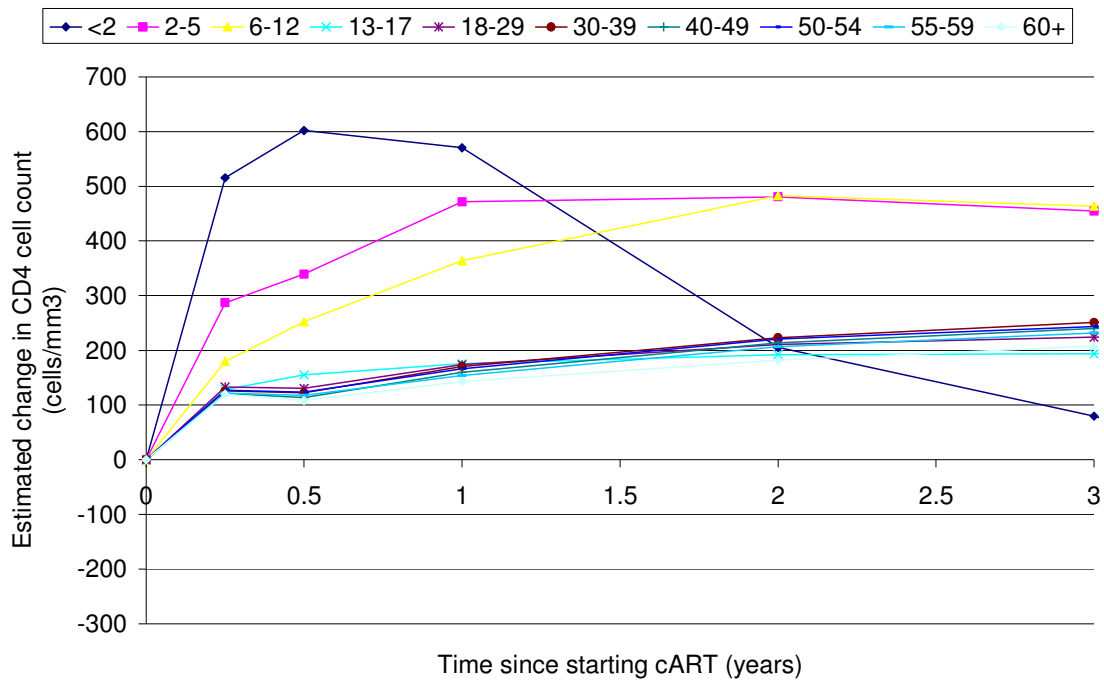
p-value (Adjusted model)

<0.0001 0.33 0.001 - 0.02 0.006 0.31 0.01

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 gender, year of starting cART, pre-cART CD4 count, pre-cART viral load, AIDS diagnosis at the time of starting cART, ethnic origin and regimen type

Figure 3 – Estimated change in CD4 count during first three years of cART according to age group



n	<2	2-5	6-12	13-17	18-29	30-39	40-49	50-54	55-59	≥60
<2	223				191			165		133
2-5	184	184			156			129		101
6-12	219		219		173			129		94
13-17	201			201	148			107		75
18-29	9134				7306			5807		4517
30-39	22410				18446			14876		11861
40-49	11588				9152			7135		5490
50-54	2693				2183			1733		1363
55-59	1656				1336			1062		817
≥60	1613				1252			961		744