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Reference: 1. Cahn P et al. Published online November 9, 2018. *Lancet*. doi:10.1016/S0140-6736(18)32462-0.

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ORIGINAL RESEARCH

Parents' attitudes to their HIV-infected children being enrolled into a placebo-controlled trial: the PENTA 1 trial

Paediatric European Network for Treatment of AIDS (PENTA)*

Objective

The study aimed to explore the experience of parents/care-givers to their child's participation in a European randomized trial of immediate (zidovudine) with deferred (placebo) antiretroviral treatment in asymptomatic children with vertically acquired HIV infection (PENTA 1 trial).

Design

One hundred and thirty-three questionnaires were distributed to parents/care-givers (68% of children in the trial) through their paediatrician prior to unblinding the individual child's therapy (zidovudine/placebo) and 84 (63% response rate) were returned.

Method and results

Thirty-six (43%) parents described moderate ($n = 30$) or great ($n = 6$) interference with everyday life. This was more frequent among parents of children whose HIV disease progressed ($P = 0.03$, Fisher's exact test) but was unrelated to ethnicity, country of origin, treatment allocated or adverse events. Invited comments suggested that concern about forgetting doses and the taste/volume of the trial medication contributed to interference with everyday life. Seventy-six (90%) parents considered information received during the trial adequate. The eight expressing dissatisfaction were recruited in the same country and five of them were among the eight (10%) who stated that they would not want to enrol their child in another trial.

Conclusion

There is a need for adequate ongoing feedback about trial progress to participating families. With increasing use of complex antiretroviral regimens, innovative ways of helping families with adherence issues require development and evaluation.

Key words: adherence, attitudes, clinical trial, paediatric HIV, parents

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Introduction

There are few studies regarding patients' perceptions about being involved in a clinical trial. In those which have been carried out in adults, close medical follow-up [1–4] and increased information and advice [5] have been cited as benefits of participation, whereas increased time getting to or spent at the clinic [1,3–5] and side-effects of the study drug have been cited as disadvantages [2,5]. There are even fewer data on the attitudes of parents to their children participating in a clinical trial. Studies in this area have focused on issues around informed consent [6–8] and characteristics of families agreeing to their children's participation in a clinical trial [9,10].

In this study, we invited parents (or primary care-givers) of children enrolled in a placebo-controlled trial of zidovudine (ZDV) therapy in asymptomatic or mildly symptomatic HIV infection to complete a short questionnaire before unblinding the individual child's therapy (ZDV or placebo). The aims of the study were to describe parents' experience of their child being enrolled in a clinical trial including the degree to which it interfered with life, and their feelings about use of placebo.

Methods

The Paediatric European Network for Treatment of AIDS (PENTA) was established in 1992 to undertake multicentre trials in HIV-infected children. The aims were to provide a

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network of paediatric centres to set up trials to answer therapeutic questions in children which could not be answered or assumed from results of trials in adults. The first trial (PENTA 1 trial) is a double-blind placebo-controlled trial comparing immediate with deferred therapy ZDV. Children were randomized to receive ZDV (immediate) or matching placebo (deferred) and followed-up at 2, 4 and 12 weeks and then 12-weekly for an average of 23 months. ZDV or placebo were available as liquid (taken by the majority of children) or as capsules, taken three times a day. At the start of the trial the dose was 600 mg/m^2/day (about 10 mL three times daily for a 7-year-old); this decreased to 360 mg/m^2/day following publication of results from a trial showing no differences in efficacy between high and lower doses of ZDV [11]. Any child experiencing clinical progression or rapidly falling immunity as measured by CD4 counts could be switched to open ZDV with the paediatrician and parents remaining blind to the original randomization. The trial was approved by the ethics committee of each participating centre.

Between 1992 and 1995, 197 vertically HIV-1 infected children with asymptomatic or mild disease who had not received prior antiretroviral therapy had been enrolled into the trial and followed for a median of 23 months. In 1995, results of adult trials showed a significant benefit of combination therapy compared with ZDV monotherapy [12–14]. Therefore, a decision was made on ethical grounds to unblind individual children in the trial, so that those on ZDV could switch to combination therapy. Prior to unblinding, parents were invited to complete a short questionnaire about their experience of participating in the trial. Follow-up of all children in the trial has continued and all questionnaires were completed and returned prior to analysis of the trial results.

Questionnaire

The questionnaire was modelled on one which was presented to patients participating in the Concorde trial (personal communication, J. Darbyshire). It was simplified and shortened in order to make it quicker for parents to complete, and thus hopefully improving the response rate. It also had to be translated into several languages, therefore the more succinct the better.

The questionnaire was sent to paediatricians caring for 133 children (68% of all children in the trial) in centres in Italy, Germany, Holland, Sweden, Canada, Brazil and UK, co-ordinated through the Medical Research Council HIV Clinical Trials Unit (MRC HIV CTU), London, UK. It was not sent to all participating centres, as some had already unblinded therapy and it was important for the questionnaire to be completed before this took place. Paediatricians were asked to invite parents or carers to fill out the questionnaire prior to telling them whether the child had received ZDV or placebo. Questions were asked on the following: the degree to which participation in the trial interfered with everyday life (scale 1–4); the worry caused by the child being on blinded therapy (scale 1–3); whether enough information was given on the progress of the trial (yes/no); what treatment they thought the child was taking (ZDV/placebo/unsure); and whether or not they would be willing for their child to be enrolled in another trial (yes/no/uncertain). Comments about the trial were also invited.

Questionnaires were identified by child's trial number only, and included no names. Data from the questionnaires were combined with key clinical data and analysed in Stata using descriptive statistics and the χ^2 test where appropriate.

Results

Eighty-four questionnaires were returned (63% response rate); six centres did not return any questionnaires. Compared with the children of parents/carers not returning question-

Table 1 Children in the PENTA 1 trial whose parents/carers were sent questionnaires

	Questionnaire returned *n* = 84	Questionnaire not returned *n* = 49
Country		
Italy	35 (42%)	22 (45%)
UK	14 (17%)	12 (25%)
Germany	2 (2%)	9 (18%)
Holland	0 (0%)	3 (6%)
Sweden	1 (1%)	0 (0%)
Canada	2 (2%)	0 (0%)
Brazil	30 (36%)	3 (6%)
Ethnicity		
White	50 (60%)	31 (63%)
Black African	20 (24%)	10 (21%)
Other	14 (16%)	8 (16%)
Mean age (years)	4.3	2.8
Sex: female	48 (57%)	32 (65%)
Adverse events		
Major	7 (8%)	7 (14%)
Minor	8 (10%)	7 (14%)
Trial drug stopped		
Disease progression	9 (11%)	16 (33%)
Adverse event-		
Major	0 (0%)	0 (0%)
Minor	1 (1%)	7 (14%)
Child refused to take medicine	6 (4%)	2 (4%)
At parents' request	6 (7%)	6 (12%)
On trial drug at end of blinded phase	65 (77%)	18 (37%)*

* Significantly different in comparison with questionnaire returned group (see text).

naires, children of responders were older (mean age 4.3 years in responders and 2.8 years in non-responders) and significantly less likely to have stopped the trial drug ($P < 0.001$, Fisher's exact test, Table 1).

Interference with everyday life and worry

Thirty-six (43%) parents/carers reported that the trial interfered to a moderate ($n = 30$) or great ($n = 6$) degree with everyday life. Compared with those reporting little or no interference ($n = 48$), a significantly higher proportion had children who transferred to open ZDV for disease progression ($P = 0.03$, Fisher's exact test, Table 2), but no relation was observed between moderate or high interference and ethnicity, country of origin, treatment allocated (ZDV or placebo) or stopping medication prior to the end of the blinded phase because of either parental request or adverse events. Frequent worry about whether the child was on ZDV or placebo was reported by 16 (19%) parents. In five (31%) children of these 16 parents/carers, disease progression to HIV symptoms or AIDS occurred compared with only four (3%) of the 68 reporting little or no worry ($P = 0.006$, Fisher's exact test, Table 2). Worry was also not associated with ethnicity, country of origin or with the occurrence of minor or major adverse events.

Information

Seventy-five (90%) parents/carers reported that they received enough information about the progress of the trial. Only eight reported that information was inadequate, and all of these were from the same country, five being from the same centre. All but one family were Caucasian. Five of the eight would definitely not want their child to enter another trial and three were unsure. There was a significant relationship between perception of lack of information and unwillingness to enrol in future trials ($P < 0.001$, Fisher's exact test).

Future trials

Fifty parents/carers (60%) stated that they would be happy for their child to be enrolled in future trials, 26 (31%) were unsure and eight (10%) would not want their child enrolled into another trial. The eight families against future involvement in trials were from the same country and four withdrew their children from the PENTA 1 trial: one for a minor adverse event and three on request by the parents (Table 3). There was only one withdrawal (child refused to take the medicine) among 50 (2%) children whose parents/carers were happy for their child to enrol in another trial, three (12%) withdrawals among those who were unsure and six (60%) among those who said that they would not be happy for their child to enrol in future trials. Thus, if the trial drug had been stopped during the trial, the parent would be more likely to be unhappy or unsure about enrolling their child into future clinical trials ($P < 0.001$, Fisher's exact test, Table 3).

Table 2 Views of parents/carers about participation in the PENTA 1 trial by child's therapy at time of questionnaire completion

	On trial drug $n = 65$	Drug stopped during trial* $n = 10$	On open drug for HIV progression $n = 9$	Total $n = 84$
Moderate/much interference with everyday life	23 (35%)	6(60%)	7 (78%)†	36 (43%)
Frequent worry	7 (11%)	4 (40%)	5 (55%)‡	16 (19%)
Inadequate information	4 (6%)	4 (40%)	0	8 (9%)

*Minor events = 1; child refusal = 3; parents'request = 6. † $P = 0.03$ for the comparison with little/no interference (see text); ‡ $P = 0.006$ for the comparison with those with little or no worry (see text).

Table 3 Parent's feelings about enrolling in future clinical trials by child's therapy at time of questionnaire completion

Parents happy to enrol children into future trials	On trial drug $n = 65$	Drug stopped during trial $n = 10$	On open drug for HIV progression $n = 9$	Total $n = 84$
Yes	44 (69%)	1 (10%)*	5 (55%)	50 (60%)
No	2 (3%)	6 (60%)	0	8 (9%)
Unsure	19 (29%)	3 (30%)	4 (44%)	26 (31%)

* $P < 0.001$ for the comparison with children whose parents were unhappy/unsure of allowing their child to enrol in a future trial (see text).

Table 4 Opinion of parents/carers about their child's randomization

	Percentage randomized to		
	Zidovudine *n* = 46	Placebo *n* = 38	Total *n* = 84
Opinion of parents/carers about randomization			
Zidovudine	19 (41%)	7 (18%)	26 (31%)
Placebo	3 (7%)	5 (13%)	8 (10%)
Unsure	24 (52%)	26 (69%)	50 (59%)

Of the 34 (41%) of parents/carers who guessed, 24 (71%) were correct and 10 (29%) were incorrect. This difference was not statistically significant ($P = 0.43$) (see text).

Zidovudine or placebo?

Forty-six (55%) children of parents/carers who returned questionnaires were on ZDV compared with 38 (45%) on placebo (Table 4). When asked to guess what therapy they thought their child had been taking, the majority stated that they were unsure. The proportion who expressed uncertainty was higher in Brazil (28/30, 94%) than in Italy (15/35, 43%) or the UK (6/14, 43%), these being the three countries with over five questionnaires completed. After allowing for country, there was no difference in ethnicity in the way this question was answered. Among those who attempted to guess their child's therapy, 24 (71%) were correct and 10 (29%) were incorrect. This was unrelated to whether they were randomized to ZDV or placebo ($P = 0.43$, Fisher's exact test, Table 4).

Invited comments

Comments were volunteered by parents/carers as to why the trial interfered with everyday life on 34% of the questionnaires, with two themes emerging. The first was in reference to the timing of trial drug doses and included comments such as: 'problems giving the drug during school term time'; 'I was worried about giving the drug at the right time'; and 'difficult always to remember'. The second was dissatisfaction with the taste and volume of the trial medication.

Comments regarding the adequacy of information given during the trial were reported on 13% of the questionnaires, and also centred around two concepts. First, parents/carers indicated that it made a difference who gave out the information. Secondly, several indicated that they would have liked more updates during the trial, especially about generated information and how it would impact on future care. It should be noted that two newsletters were circulated during the course of the trial but neither, of course, contained any results.

Discussion

We have explored the perceptions of parents/carers to their children's participation in a placebo-controlled trial prior to unblinding the treatment arm in which the child was placed. All children enrolled in the study were vertically HIV-infected, so the mother and possibly other family members were also infected. The majority of children would have been unaware of their HIV diagnosis. It is of relevance that, during the course of the trial, there was adverse press publicity around the use of ZDV for HIV infection in some European countries [15].

Non-responders

Several studies have reported on attitudes of adult participants to therapeutic [1–4] and prevention [5] trials. However, those reporting on attitudes of parents/carers to their children's involvement in trials have focused mainly on issues around consent [6–8]. In our study, there were some differences between children of parents/carers who returned questionnaires and those who did not. Children of non-responders were younger and a higher proportion had stopped the trial drug, the most common reason being for disease progression. It is possible that in these cases, where children had already been transferred to open ZDV, parents could not see the relevance of some of the questions asked or the paediatricians did not give them the questionnaire. It is unclear whether a higher response rate would have affected the results, although as children who had progressed were over-represented among non-responders, interference with everyday life might have been higher.

Interference with everyday life and worry

Increased worry about what therapy the child was receiving and interference with everyday life were more frequent in children whose HIV disease progressed. This may have related more to events surrounding HIV disease and starting open ZDV rather than the trial itself.

Adverse events did not appear to cause worry about therapy, possibly because the great majority were laboratory events which did not cause symptoms in the children. Neither worry nor interference with everyday life appeared to be so prominent for parents of well children despite adverse publicity around ZDV, which was prominent in some countries around this time [15]. Review of the data

collected during the course of the trial on 140 children whose parents were invited to participate in the trial but decided not to showed that only four parents (3%) stated explicitly that they were concerned with the use of placebo; a further 20 were against clinical trials in general and 68 had concerns about giving their child medication. Thus concern about placebo did not appear to be a major issue among families refusing entry into the trial. Increased clinic visits have been reported as a common disadvantage to participation in adult trials [1–5]. However, few extra clinic visits were required in this trial, which was planned to follow standard clinical practice for monitoring well HIV-infected children with mild or no symptoms. Nevertheless, among children remaining on the trial drug, 35% reported moderate to great interference with everyday life with only one antiretroviral drug. This is particularly pertinent now that complex multidrug regimens including three or more drugs are being used.

Information

Overall, the majority of parents/carers reported being satisfied with information they received about the trial. Where dissatisfaction was expressed, this was associated both with stopping trial treatment in the absence of disease progression or adverse events, and to a stated disinclination to join future trials. The majority were from the same centre and all were from the same country. All centres had access to the same documented information when discussing the trial with participants. It is possible that these parents were in contact with each other and jointly received some other adverse information during the course of the trial. The proportion of parents/carers reporting that they would be happy for their children to participate in future trials (60%) was similar to reports from adult trials [1–5]. As in the study of Hudmon *et al.* [5] we observed no association between definite disinterest in future trials and perceived negative experiences (worry and interference with everyday life) in this trial. However, there was a clear association between concern over perceived lack of information available about the trial and unwillingness among a minority of parents/carers to allow their child to participate in future trials.

A limitation of this study is that the respondents to the questionnaires were not asked to state their relationship to the child. However, whereas the majority of children in the UK and Italy were cared for by parents, primarily the mother, anecdotally we were aware that many of the children in Brazil were cared for by extended family members or others. The fact that mothers were themselves infected with HIV could be one reason why UK and Italian respondents were more willing to guess the therapy that their child was taking, as they would be more knowledgeable about ZDV.

Conclusion

Overall, parents and carers of children enrolled in this randomized, placebo-controlled trial reported fairly positively about their experience. Interference with everyday life and worry were associated with disease progression in the child and appeared to relate to concern about adherence and characteristics of the drug. Adherence could be helped by the use of diaries, drug schedules or other aides to help carers to remember to give the drugs. Lowering the frequency and volume of medication as well as making it as palatable as possible for children is also clearly desirable where feasible. There is a clear need for adequate and ongoing information on the progress of a trial to be fed back to parents/carers and children where appropriate. Further studies to evaluate the views of parents who enrol their children into clinical trials are required. Studies are also required to assess adherence and the aids which are developed to enhance it. This is of particular importance with increasing use of multiple and more complicated combination antiretroviral drug therapies for children and for other family members with HIV infection.

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References

1 Mattson ME, Curb JD, McArdle R, AMIS Research Group BHAT Research Group. Participation in a clinical trial: the patients' point of view. *Control Clin Trials* 1985; **6**: 156–157.

2 Tangrea JA, Adrianza ME, Helsel WE. Patients' perceptions on participation in a cancer chemoprevention trial. *Cancer Epidemiol Biomarkers Prev* 1992; **1**: 325–330.

3 Nasco EM, Leonard AD. Assessment of participant satisfaction in a clinical trial by an exit questionnaire. *Control Clin Trials* 1994; **15**: 43S–44S (abstract).

4 Hezlova MJ, Blackburn GH, Bradley EJ, Rogers WJ. Patient perception of a long-term clinical trial: experience using a close-out questionnaire in the studies of left ventricular dysfunction (SOLVD) trial. *Control Clin Trials* 1994; **15**: 284–293.

5 Hudmon KS, Stoltzfus C, Chamberlain RM, *et al.* Participants' perceptions of a Phase I colon cancer chemoprevention trial. *Control Clin Trials* 1996; **17**: 494–508.

6 Harth SC, Thong YH. Parental perceptions and attitudes about informed consent in clinical research involving children. *Soc Sci Med* 1995; **41**: 1647–1651.
7 Susman EJ, Dorn LD, Fletcher JC. Participation in biomedical research: the consent process as viewed by children, adolescents, young adults and physicians. *J Pediatr* 1992; **121**: 547–552.
8 Kamps WA, Akkerboom JC, Nitschke R, *et al*. Altruism and informed consent in chemotherapy trials of childhood cancer. Special Issue. Psychosocial aspects of chemotherapy in cancer care: the patient, family and staff. *Loss Grief Care* 1987; **1**: 93–110.
9 Harth SC, Thong YH. Sociodemographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study. *Br Med J* 1990; **300**: 1372–1375.
10 Autret E, Dutertre JP, Barbier P, *et al*. Parental opinions about biomedical research in children in Tours, France. *Dev Pharmacol Ther* 1993; **20**: 64–71.
11 Brady MT, McGrath N, Brouwers P, *et al*. Randomized study of the tolerance and efficacy of high- versus low-dose zidovudine in human immunodeficiency virus-infected children with mild to moderate symptoms (AIDS Clinical Trials Group 128). *J Infect Dis* 1996; **173**: 1097–1106.
12 DELTA Co-ordinating Committee. DELTA: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996; **348**: 283–291.
13 Hammer SM, Katzenstein DA, Hughes MD, *et al*. A trial comparing nucleoside monotherapy with combination therapy in HIV infected adults with CD4 counts between 200 and 500 per cubic millimeter. *N Engl J Med* 1996; **335**: 1081–1090.
14 Saravolatz LD, Winslow DI, Collins G, *et al*. Zidovudine alone or in combination with Didanosine or Zalcitabine in HIV infected patients with acquired immunodeficiency syndrome or fewer than 200, CD4 cells per cubic millimeter. *N Engl J Med* 1996; **335**: 1099–1106.
15 Editorial (anonymous). Zidovudine for mother, fetus and child: hope or poison. *Lancet* 1994; **344**: 207–209.

Appendix

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