When do children convert from liquid antiretroviral to solid formulations?

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Key words
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Antiretroviral
Formulation
Long-term treatment
Retention

Abstract
Background: Liquid formulations are usually regarded as the gold standard in paediatric formulation; but sometimes, liquid formulations have stability and taste problems as well as being inconvenient for travelling. Therefore, for the management of long-term illness, some older children, parents and clinicians would prefer to use solid formulations. However, there is a lack of studies to investigate the age at which children are converted from liquid to solid formulations.
Objectives: (1) To investigate the age range at which children convert from liquid antiretroviral drug formulations to solid formulations, the formulations are abacavir, didanosine, lamivudine, stavudine, and zidovudine. (2) To calculate how long children stay on each of five UK liquid formulations (retention time) and factors affecting the retention times of the above liquid formulations.
Method: This was a retrospective medical records survey at Great Ormond Street Hospital for Children, London, United Kingdom. Patients' treatment details were entered into SPSS for Windows v. 11.0 and the retention times for the above liquid formulations were calculated i.e., from initiation of the liquid treatment to conversion to solid preparation. The retention times of different preparations were then compared using Cox regression analysis.
Results: A total of 92 patients are included in the analysis. The overall average age at conversion was 7.3 years (95% CI 6.3–8.2). Patients on stavudine were more likely to switch to the corresponding solid dose form than the other four medicines ($P < 0.001$); more than 50% of patients on stavudine switched to solid formulation after nine months of treatment, however, less than 25% of patients on other formulations switched during the same period.
Conclusion: Children taking antiretroviral liquid preparations change to solid dose forms at approximately seven years of age. However, for stavudine, children are more likely to take the solid form at an earlier age.

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Introduction

Most young children find taking solid dosage forms difficult. Liquid preparations are regarded as the gold standard in paediatric medicines for young children[1–3]. However, the reaction of young patients and their carers to medication are also governed by other factors such as tolerability, taste, dose volume[4,5] and the frequency of administration[6]. One in two parents report their child has refused to take medications[7]. Family dynamics have an important impact on therapy; the support from parents and their perception has important effects on compliance[8,9].

In general, children and carers prefer a liquid formulation to crushing and dispersing a solid dose formulation; but sometimes, liquid formulations have stability and taste problems as well as being inconvenient for travelling. Therefore, for the management of long-term illness, some older children, parents and clinicians would prefer to use solid formulations. However, there is a lack of studies to investigate the average age at which children could manage to take solid formulations. In this study, we studied age ranges at which children are converted from liquid to solid formulations in five nucleoside reverse transcriptase inhibitors (NRTIs) over a period of eight years. NRTIs are essential components of highly active antiretroviral therapy[10] and patients are on these drugs for a number of years thus rendering them suitable for study.

Objectives

(1) To investigate the age range from which children convert from liquid antiretroviral drug formulations to solid formulations; the formulations are abacavir, didanosine, stavudine, lamivudine and zidovudine.
(2) To calculate how long children stay on each five UK liquid formulations (retention time) and factors affecting the retention times of the above liquid formulations.

Method

Setting

The study was undertaken at Great Ormond Street Hospital for Children, a specialist HIV referral centre in the UK.

The computerized dispensing records at Great Ormond Street Hospital for Children pharmacy were searched to identify patients who had been initiated on one of the five liquid antiretroviral formulations between May 1996 and May 2004. The drugs investigated were abacavir, didanosine, lamivudine, stavudine and zidovudine.

Ethics

Opinion from the local research ethics committee was sought when the study commenced in 2003; ethics application was not required according to the Standard Operating Procedure of the Hospital.

Data collection

From the dispensing record, the following data were obtained:

(1) Age of the patient when the liquid antiretroviral formulation(s) started;
(2) Gender of the patient;
(3) The start date of liquid antiretroviral formulation(s);
(4) The date of conversion from liquid formulations to solid formulations
(5) The date of the latest dispensing for patients who continued on liquid formulation or the date of cessation of treatment. These patients were

classified as censored patients i.e., patients who had not experienced the conversion.

Exclusion criteria

(1) As pharmacy dispensing records started in 1996, patients who started antiretroviral therapy prior to 1996 were excluded.
(2) Patients who had been exposed to or started the liquid treatment outside of the Centre were also excluded as the start date of the treatment was unknown and retention times could not be calculated.
(3) Patients who only attended the Clinic temporarily (less than six months) were also excluded as the outcome data was not available.

The data was then entered into the SPSS for Windows V11 for analysis.

Analysis

For children converted from liquid to solid formulation, the average age and 95% CI were calculated.

The exact time of conversion (from liquid to solid) of all cases is not known because some patients were still receiving the liquid treatment (it is called 'censored' patients in statistical terms) when data were analysed. Furthermore, as patients have entered the study at different times, some recent entrants may still be receiving treatment but have been observed only for a short time. Their treatment time may be less than those patients admitted early in the study who have since stopped the treatment. Traditional statistical methods do not take censored patients into consideration; therefore Cox regression analysis was used[11] to study the retention time of individual liquid preparations. Cox regression allows estimation of the retention probability (probability of continuing liquid treatment in this study) and study of the effects of possible confounding factors such as age and gender; furthermore, it also allows construction of a retention curve (probability of continuing liquid treatment vs. time) to compare between different drugs. This method has been used to study the long-term effectiveness of antiepileptic drugs[12–15].

Results

A total of 92 patients were identified as having been exposed to at least one of the five drugs and their data are included in the analysis.

The overall average age at conversion was 7.3 years (95% CI 6.3–8.2). Average age at conversion of individual drugs is shown in Table 1; it also shows that children on stavudine were significantly younger (3.6 year-old (95% CI 2.7–4.6)) when they converted to solid formulation.

Cox regression has shown that the age when antiretroviral liquid medication started has a marginal significant effect ($P = 0.051$) on the retention time i.e., the younger the patient starts the treatment, the more likely they are to stay on longer. Gender has not shown to have a significant effect on retention time ($P > 0.1$); however, the Cox regression in Table 1 has shown that patients on stavudine are more likely to switch to the corresponding solid dose forms than the other four medicines ($P < 0.001$. The Cox regression estimated that more than 50% of patients on stavudine would switch to solid formulation after nine months of treatment, however, less than 25% of patients on other formulations switched during the same period of time.

Figure 1 shows the estimated survival curves for retention on the treatment, the Cox regression has adjusted the effect of age.

Discussion

Our research group has been questioned repeatedly by formulation scientists from the pharmaceutical industry on the appropriate age to convert from liquid formulation to solid in children with long-term conditions; it is important for them to know this factor so that they can produce appropriate paediatric formulations whilst taking the dose, taste, and convenience for children and parents into consideration. Unfortunately, we were unable to identify published literature to answer this question and it inspired us to conduct this study.

The results have demonstrated that some children were using solid formulations of antiretroviral treatment at a young age. The overall average age at conversion was 7.3 years; it probably reflects that this is the appropriate age for children on long-term treatment such as antiretroviral treatment to consider the use of solid formulations. Past reports have demonstrated that it is possible to teach a six-year old[16] and developmentally disabled children as young as four and a half-years old to swallow a solid dose form[17].

Identification of patients on stavudine converted to a solid formulation was not expected at such a young age (3.6 year-old (95% CI 2.7–4.6)). The Cox regression model has shown that there are statistical

Table 1 *Demographic detail and outcomes of the patients*

Drug	*Number of patients (boy/girl)*	*Mean start age of the liquid formulations (95% CI)*	*Number of patients changed to solid formulations (%)*	*Mean age change from liquid to solid formulation (95% CI)*	*Relative risk of conversion to solid formulation compared to stavudine (95% CI)*
Stavudine	22 (10/12)	2.9 (1.8–4)	16 (73)	3.6 (2.7–4.6)	N/A
Abacavir	25 (14/11)	8.1 (5.2 –10.9)	10 (40)	9.2 (6.7–11.7)	0.249 (0.106–0.581) $P < 0.001$
Didanosine	27 (11/16)	5.8 (3.5–8.1)	13 (48)	7.2 (5–9.5)	0.361 (0.17–0.767) $P < 0.01$
Lamivudine	74 (42/32)	6.5 (4.8–8.2)	15 (20)	10 (8.5–11.4)	0.091 (0.043–0.193) $P < 0.001$
Zidovudine	34 (19/15)	4.0 (1.8–6.2)	7 (21)	6.9 (5.5–8.4)	0.078 (0.03–0.204) $P < 0.001$

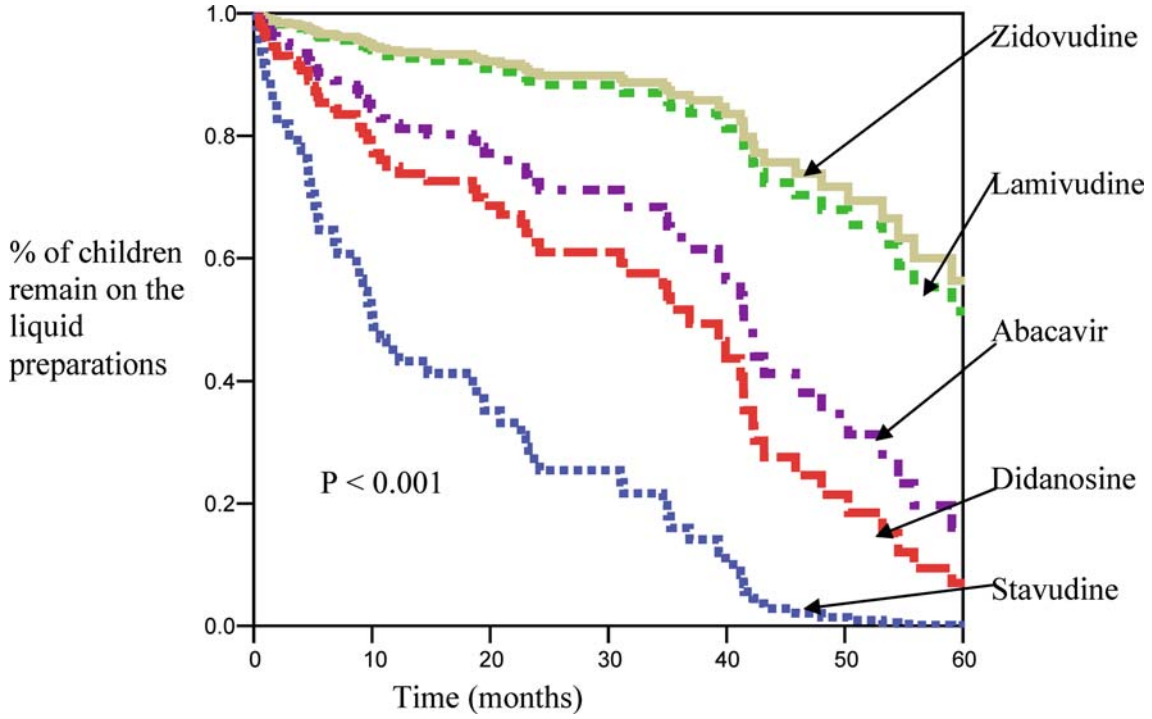

Figure 1 *Percentage of children remaining on liquid HIV formulation.*

differences between stavudine and other antiretroviral liquid preparations. The regression estimated that nearly half of the patients on stavudine convert to a solid dose within nine months of starting therapy, whereas those treated with didanosine take 37 months to convert and most patients on lamivudine and zidovudine stay with the same formulation over the study period. Furthermore, the pharmacy computer record indicated that three patients open up the stavudine capsules, disperse the contents and draw out a fraction of the solution corresponding to the dose, rather than using the licensed liquid formulation. This observation suggests the liquid formulation of stavudine may not be well received by patients and/or parents.

The mean start age of each liquid formulations varied from 2.9 to 8.1 years. Some drugs were unavailable at the start of the study which lasted for eight years. It is inevitable that some newer drugs such as abacavir had a higher mean start age. The start age of treatment should have an inverse relationship with the retention time of any given drug. The older the age of the child starting treatment, the shorter the time it takes to switch to solid dose formulation. However, such a relationship is not observed when comparing liquid stavudine with other

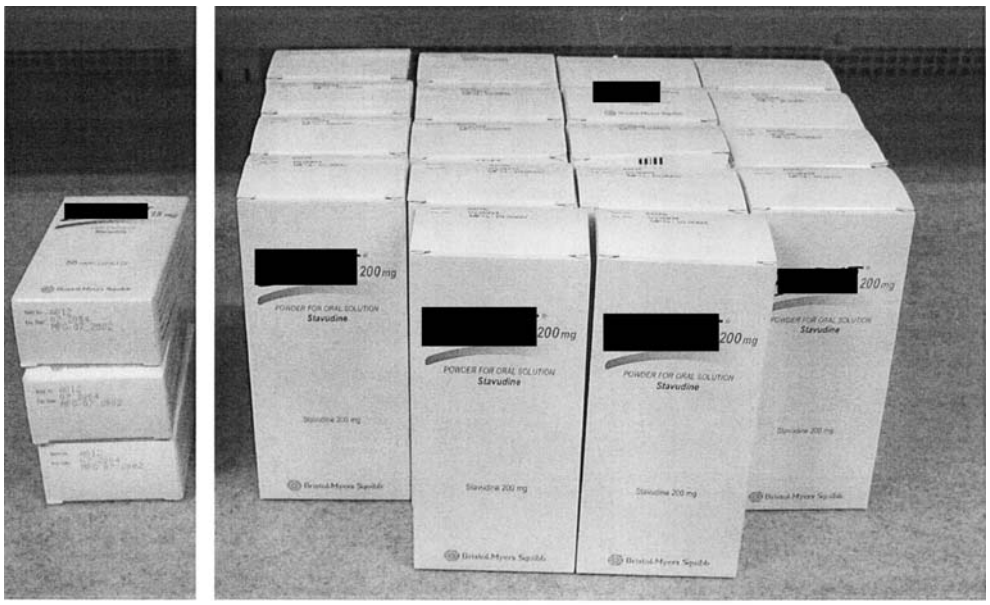

Figure 2 *Three months treatment of stavudine.*

liquid antiretroviral drugs. The mean start age of stavudine was lower than other drugs, the retention time of stavudine liquid formulation was the shortest; it suggests other important factors are in operation.

Stavudine comes in a powder form and once reconstituted is stable for 30 days stored between 2 and 8 °C. The normal paediatric dose is 1 mg/kg and for a five-year-old, the daily dose is 40 ml a day. One pack only lasts for six days, and therefore for a three-month period, the carer has to transport home 18 containers and will have to perform 17 reconstitutions. However in comparison, three small boxes of capsules could cover the same period of treatment (see Figure 2).

Dose volume is another factor that could affect acceptability of the formulation; a large dose volume is unlikely to be appealing to the children. The daily dose volumes for a 20 kg child are stavudine (40 ml), abacavir (16 ml), didanosine (12 ml), lamivudine (16 ml), and zidovudine (22 ml). The large dose volume of stavudine liquid preparation may be a deterrent for patients and carers but future study is required to verify this observation.

Children should be given a wider choice of liquid and solid dose formulations to cater for their changing needs.

Summary

Children taking antiretroviral liquid preparations change to solid dose forms at approximately seven years of age. However, for stavudine, children are more likely to take the solid form at an earlier age.

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