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ORIGINAL RESEARCH ARTICLE

A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand

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Summary: Scaling up of antiretroviral treatment (ART) for children in countries like Thailand will require decentralization and management by non-specialist doctors. We describe (a) the formulation of a standardized drug dosage table to facilitate antiretroviral drug (ARV) prescriptions for children, (b) the acceptability of such a table among doctors and (c) the safety and efficacy of drug doses in the table.

Acceptability was assessed using a questionnaire. Safety and efficacy were assessed on the basis of incidence of adverse effects and virological response to treatment, respectively.

Of all doctors ($n = 18$), 17 (94%) found that the table was practical to use, avoided miscalculations and made them more confident with prescriptions. Of 49 children prescribed ARVs, less than 5% had adverse side-effects. All ARV-naïve children achieved undetectable viral loads within six months of ART.

In our setting, a standardized drug dosage table provided a simple and reliable tool that facilitated ARV prescriptions for children.

Keywords: HAART, drug dosages, paediatric formulations, Thailand

Introduction

In 2001, the Thai Ministry of Public Health began offering highly active antiretroviral treatment (HAART) to children with HIV/AIDS in Thailand. The programme eventually aims to reach all of the estimated 21,000 children[1] with HIV/AIDS needing HAART. In order to achieve this, there will be a need to decentralize treatment to district hospitals where non-specialists will have to prescribe HAART.

A number of obstacles hamper this process.

- Doctors at district level, inexperienced with prescribing HAART, lack confidence due to unfamiliar and complex dose expressions. Drug dosages are expressed in terms of body surface area for some drugs, but by body weight for others. Dosage calculations become time-consuming and with a high-patient load, prone to human error. Mistakes also often occur in the measurement of children's height.
- International[2–4] and Thai[5] recommendations give broad and inconsistent dosage ranges for some antiretroviral (ARV) drugs, which thus appear vague (Table 1). Standardization of prescriptions thus becomes difficult.
- Paediatric syrup formulations where available are expensive, have a short shelf-life, and are difficult to store. Available syrups are also generally of low concentration and thus children have to swallow large volumes of unpalatable liquid, which often induces vomiting. For example: a child weighing 12 kg and on a triple therapy regimen of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP) would need to swallow a total of 27.5 mL (12.5 mL of AZT, 5 mL of 3TC and 10 mL of NVP) of syrup twice daily. Many caretakers of children are old and illiterate and cannot measure such different volumes of different syrups. Many even ask for capsules or tablets which are easier to manage than syrups. These are also less obvious when being carried home. Tablets or capsules are, however, rarely available in paediatric dosages.
- In practice, unrealistic prescriptions for children are written, based on fractions of adult tablet formulations. Examples of required

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Table 1 Recommended paediatric dosage for zidovudine (AZT)

180 mg per m^2 of body surface area every 12 h[2,3]
90 mg per m^2 of body surface area to 180 per m^2 of body surface area every 6–8 h[4]
160 mg per m^2 of body surface area every 8 h[5]

Table 2 Examples of recommended antiretroviral dosages expressed as fractions of tablet formulations[6]

Child 3–4 kg:	Child 10 kg:
3TC 1/10 tablet BID	AZT $\frac{3}{4}$ Caps BID
d4T: 1/8 tablet BID	3TC: $\frac{1}{4}$ tablet BID
NVP: 2.5–4 mL BID	NVP: 5.5–9 mL BID

BID=twice daily; 3TC=lamivudine; d4T=stavudine; NVP=nelfinavir; AZT=zidovudine

fractions of tablets[6] are given in Table 2. Parents or caretakers cannot accurately break off such fractions of a tablet or open capsules to dissolve a prescribed portion of the powder. Furthermore, some tablets such as Epivir® (3TC) tablets are not scored and breaking off fractions of such tablets accurately is difficult. Moreover, the effect of breaking tablets, not designed to be broken, or of opening capsules on bioavailability is unknown. Thus, achieving accurate dosing for children is often impossible in practice.

- Once children start antiretroviral treatment (ART), weight gain necessitates ongoing dosage adjustment. Fine tuning of such adjustments is impossible due to the limited range of available formulations and seems irrelevant, considering the wide ranges of currently recommended dosages.[2–5] Moreover, blood levels of some drugs depend less on weight or body surface than on genetic factors (nevirapine [NVP]) and renal clearance (lamivudine [3TC] and stavudine [D4T]).

ARV prescriptions for children in resource-poor settings need to be simplified and made more user-friendly. In our setting, a standardized drug dosage table provided a simple and reliable tool to facilitate prescriptions among paediatricians and general practitioners (GPs). This report gives an overview of the drug dosage table in terms of (a) how it was formulated, (b) its acceptability among doctors and (c) safety and efficacy of doses in the table.

Materials and methods

Setting

The drug dosage table has been used since February 2002 in one provincial hospital (PraChomklao) and two district hospitals (Ban Laem and Kuchinarai hospitals). These hospitals started HAART in children with the support of a non-governmental organization (Médecins sans Frontieres [MSF]).

The standard first-line triple regimen for children was zidovudine (AZT)/3TC/NVP. In case of severe adverse drug reactions to AZT or NVP, these were replaced with D4T or efavirenz (EFV), respectively. The standard second-line ARV regimen for children was a combination of D4T, didanosine (DD1) and nelfinavir (NFV). The regimens for experienced children were individualized.

All ARV drugs were registered in Thailand. EFV and nelfinavir were originator brand products, while all the others were generics produced by the Government Pharmaceutical Organization (GPO). The choice of drugs and regimens was in accordance with Thai national guidelines.[5]

The drug dosage table

Formulation of the drug dosage table in 2001, and a 2003 revision, took into account international[2–4] and Thai[5] dosage guidelines and the availability of drug formulations. The upper and lower values of recommended dosages for ARV drugs available in Thailand were expressed for body weight ranges of 5 kg for children weighing up to 30 kg, and for ranges of 10 kg for adolescents and adults weighing up to 60 kg. Where different guidelines recommended different dosages, we chose the median recommended dose. This is the case with AZT (Table 1).

For drugs where dosage is based on body surface area, the maximum height for the upper value of each weight range and the minimum height for the lower value were derived from existing growth charts of children in Thailand[7] (allowing for a standard deviation of -1.5 to $+1.5$). Upper and lower limits of surface area were then calculated for each weight range using Mosteller's formula.[8] The upper and lower doses for each weight range were then easily determined and a feasible dosage between these limits was included in the table.

Because of lack of paediatric formulations, or in order to include a feasible dosage in the table, some drugs are relatively over or under dosed in the table in some weight ranges. For example, in the case of NVP, for children weighing between 15 and 19 kg, using WHO[2] and PENTA[3] guidelines would result in a dose of 150 mg twice daily. Using tablet formulations, we chose to include a dose of half a tablet (100 mg) twice daily, below the median recommended dosage, but still within the range recommended by the American Paediatric Guidelines[4] and also by Boehringer Ingelheim.

To facilitate drug administration, the dosages were expressed as either half or whole tablets or in the case of syrups as half (2.5 mL) or whole (5 mL) medicine spoonfuls. In our experience, elderly caretakers cannot be expected to break smaller proportions of tablets or use syringes. We generally expressed doses as once or twice daily, avoiding three times a day dosing. Some boosted protease inhibitor dosages are not included in international

guidelines. For these we used evidence from pharmacokinetic studies.[9,10] The table does not include dosages for small infants as we feel that clinical management of neonates should be the responsibility of specialists.

Acceptability among doctors

A structured questionnaire that was pre-tested was used to gather information on the use of the drug dosage table among all doctors working in the PraChomKlao hospital in October 2003. This hospital was chosen for the survey as most children on ART are being followed up here. The hospital also has the largest numbers of doctors including several GPs. A questionnaire was given to the doctors 10 months after the ARV table was introduced.

Specific information that was sought included whether or not the table was simple to understand, practical to use, helped avoid miscalculations of doses and whether it facilitated ARV prescriptions. The responses were filled up in an anonymous manner and analysed using the SPSS software (SPSS Inc., Chicago, IL 60606, USA).

Safety and efficacy of drug doses

All children placed on ARVs were followed up on a two-weekly basis for the first month, then on a monthly basis thereafter. Children were monitored for adverse side-effects at each follow-up visit and these were recorded on the patient file. Care-takers (and children who were old enough to understand) were made aware of the potential side-effects of drugs contained in a particular HAART regimen and were asked about the side-effects on each follow-up visit. A systematic physical examination was also conducted. A list of known side-effects was made available to all clinicians, who were required on a systematic basis to enquire about the presence or absence of a known side-effect. All children had a full blood count (including haemoglobin) and a liver function test (ALAT) done at baseline and then on a monthly basis in order to monitor AZT-induced anaemia and the development of hepatitis, respectively. Serum creatinine and amylase were also assessed at baseline and subsequently every 12 months. Clinicians could also request additional laboratory investigations on the basis of clinical suspicion of side-effects.

Additional information on side-effects was obtained through counsellors and nurses who made home visits between scheduled clinic visits. A protocol for the management of adverse side-effects was available and both the medical and support team were trained on its recognition and management. We used the incidence of adverse drug reactions to assess safety of drug doses prescribed using the dosage table.

CD4 levels were assessed before initiating HAART. Viral HIV-RNA assays were not done at baseline but at six months after initiating ART and then every six months thereafter. This parameter was used to assess response to ARV drugs (efficacy). The cost of all laboratory assays was covered by the Thai Ministry of Public Health or MSF.

Results

Characteristics of the study population

Between February 2002, and November 2003, a total of 49 children and young adolescents (median age eight years, range 3–12 years) were prescribed ARVs using the drug dosage table. Their median weight was 15 kg (range 10–34 kg). On initiation of ART, 28 (57%) children had a CD4 percentage (%) ranging between 0% and 5%, 19 (39%) had a range of 5–15%, while in two (4%) patients the CD4% ranged between 15% and 20%.

The drug dosage table

Table 3 shows the drug dosage table that was formulated in Thailand.

Acceptability of the drug dosage table among doctors

A total of 18 doctors which included 14 GPs and four paediatricians were involved in the study. Twelve (67%) doctors had treated HIV-positive children for opportunistic infections including cotrimoxazole and fluconazone prophylaxis before, but had no experience prescribing HAART. Six doctors (including the four paediatricians) had prescribed ARV drugs before albeit mono or dual ARV therapy without using a standardized drug table. All doctors completed the questionnaire. Seventeen (94%) found the dosage table simple to understand and practical to use, 17 (94%) felt it avoided miscalculations in dosage calculations and 15 (83%) felt that it facilitated prescriptions for children and made them more confident in prescribing ARVs. Fifteen (83%) doctors found that the one page drug dosage table was portable and convenient. Seventeen doctors wished to continue using the table. All the six doctors who had previously prescribed ARVs gave favourable responses.

Safety and efficacy

Individuals were followed up for a median period of nine months (range 2–21 months). Four children who had been very ill on admission had died of complicated opportunistic infections between one and six weeks of initiation of HAART and one child

Table 3 HIV-drug doses related to body weight

Non-proprietary name	Proprietary name	Strength	Neonatal	5–9 kg	10–14 kg	15–19 kg	20–24 kg	25–29 kg	30–39 kg	40–49 kg	50–59 kg	>60 kg
Cotrimoxazole	Bactrim	TMP 80/SMX 400 mg		1/2 tab OD	1 tab OD	1 tab OD	1 tab OD	2 tab OD	2 tab OD	2 tab OD	2 tab OD	2 tab OD
	Co-trim*	TMP 40 mg/5 mL	3/15 mg/kg BID	5 mL OD	10 mL OD	15 mL OD	15 mL OD					
Fluconazole	Biozole*	50, 100, 200 mg caps			50 mg OD	100 mg OD	100 mg OD	100 mg OD	400 mg/week	400 mg/week	400 mg/week	400 mg/week
Fluconazole	Diflucan	50, 100, 200 mg caps			50 mg OD	100 mg OD	100 mg OD	100 mg OD	150 mg OD	200 mg OD	200 mg OD	200 mg OD
Zidovudine (AZT)	Antivir*	100 mg caps			1 caps TID	1 caps TID	2 caps BID	2 caps BID	2 caps BID			
	Retrovir	300 mg tab								1 tab BID	1 tab BID	1 tab BID
		10 mg/mL	2 mg/kg QID	7.5 mL BID	12.5 mL BID	17.5 mL BID						
Lamivudine (3TC)	Lamivir*	150 mg tab			1/2 tab BID	1/2 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID
	Epivir	10 mg/mL	2 mg/kg BID	2.5 mL BID	5 mL BID	7.5 mL BID	10 mL BID	12.5 mL BID				
AZT+3TC	Zilarvir*	300+150 mg tab								1 tab BID	1 tab BID	1 tab BID
Didanosine (DDI)	Divir*	30 mg (=25 mg)	50 mg/m2 BID	1 sachet OD+	1 sachet OD							
		60 mg (=50 mg)		1 sachet OD	+							
		115 mg (=100 mg)			1 sachet OD							
		170 mg (=150 mg)				1 sachet OD						
		230 mg (=200 mg)					1 sachet OD	1 sachet OD				2 sachets OD
		285 mg (=250 mg)							1 sachet OD	1 sachet OD	1 sachet OD	
Stavudine (D4 T)	Stavir*	15 mg caps			1 caps BID							
	Zerit	20 mg caps				1 caps BID	1 caps BID					
		30 mg caps						1 caps BID	1 caps BID	1 caps BID	1 caps BID	
		40 mg caps										1 caps BID
		1 mg/mL		7.5 mL BID	12.5 mL BID	17.5 mL BID						
Abacavir (ABC)	Ziagen	300 mg mg tab				1/2 tab BID	1/2 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID
		20 mg/mL		2.5 mL BID	5 mL BID	7.5 mL BID	10 mL BID	12.5 mL BID				
Nevirapine (NVP)	Neravir*	200 mg tab			1/2 tab BID	1/2 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID	1 tab BID
	Viramune	10 mg/mL	200 mg/m2 BID	7.5 mL BID	10 mL BID	15 mL BID	17.5 mL BID					
Efavirenz (EFV)	Stocrin	50 mg caps				1 caps OD +	2 caps OD +	3 caps OD +				
		200 mg caps			1 caps OD	1 caps OD	1 caps OD	1 caps OD	2 caps OD	3 caps OD	3 caps OD	3 caps OD
AZT+3TC+NVP	GPO-vir*	150+30+200 mg tab						1 tab BID	1 tab BID	1 tab BID	1 tab BID	
		150+40+200 mg tab										1 tab BID
Ritonavir (RTV)	Norvir	100 mg caps			2 caps BID	3 caps BID	3 caps BID	4 caps BID	4 caps BID	5 caps BID	6 caps BID	6 caps BID
		80 mg/mL		2 mL BID	2.5 mL BID	3.5 mL BID	4 mL BID	5 mL BID	5 mL BID			
Indinavir (IDV)	Crixivan	200 mg caps		1 caps BID			1 caps BID +	1 caps BID +		1 caps BID +		
		400 mg caps			1 caps BID	1 caps BID	1 caps BID	1 caps BID	2 caps BID	2 caps BID	2 caps TID	2 caps TID
Nelfinavir (NFV)	Viracept	250 mg tab	75 mg/kg BID	2 tab BID	3 tab BID	4 tab BID	5 tab BID	5 tab BID	5 tab BID	5 tab BID	5 tab BID	5 tab BID
Saquinavir (SQV)	Fortovase	200 mg SGC		2 caps TID	3 caps TID	4 caps TID	5 caps TID	6 caps TID	6 caps TID	6 caps TID	6 caps TID	6 caps TID
										or 8 caps BID	or 8 caps BID	or 8 caps BID
Boosted RTV+SQV		100 mg caps RTV +								1 caps BID +	1 caps BID +	1 caps BID +
		200 mg SQV SGC/HGC								5 caps BID	5 caps BID	5 caps BID
Boosted RTV+SQV		100 mg caps RTV +								1 caps OD +	1 caps OD +	1 caps OD +
		200 mg SQV SGC								8 caps OD	8 caps OD	8 caps OD
Boosted RTV+ IDV		100 mg RTV								1 caps BID +	1 caps BID +	1 caps BID +
		400 mg caps IDV								1 caps BID	1 caps BID	1 caps BID

*Produced by the Government Pharmaceutical Organisation, Thailand
OD=once a day; BID=twice a day; TID=three times a day; QID=four times a day
2.5 mL=½ spoon; 5 mL=one spoon; 7.5 mL=1½ spoon; 10 mL=two spoons; 12.5 mL=2½ spoons; 15 mL=three spoons; 17.5 mL=3½ spoons

Table 4 Incidence of adverse drug reactions in children placed on antiretroviral drugs

Drug	No. of children	Adverse drug reactions	Comments
Zidovudine	43	3 (7%) anaemia	All switched to stavudine
Didanosine and/or stavudine	12	—	No cases of neuropathy or pancreatitis
Nevirapine	26	1 (4%) transient mild rash (grade 1)	Nevirapine was continued
		1 (4%) persistent moderate (grade 2) rash	Switched to efavirenz
			No raised transaminase above 100 IU/L
Efavirenz	16	1 (6%) severe drowsiness	Switched to nevirapine
Nelfinavir	7	—	No cases of diarrhoea

died from accidental electrocution at home. Two children had changed residence and were lost to follow-up. One child simply refused to continue to take medication and neither the medical team nor the care-taker were unable to convince her otherwise. HAART was eventually stopped in this child.

Table 4 shows the frequency and types of adverse drug reaction side-effects seen in the 49 children and adolescents who were started on ARV. Three (7%) of 43 individuals on AZT developed anaemia that required a switch to D4T. There were two (8%) of 26 individuals who developed a dry maculopapular rash while on NVP. In one child the rash was transient and NVP was continued without problems, while in the other in whom it was persistent for over one month NVP had to be switched to EFV. One (6%) of 16 children on EFV developed severe drowsiness and was switched to NVP. The child improved and continued on NVP. None of the children required admission to hospital for management and there were no deaths that were attributed to drug-related side-effects.

HIV-RNA assays assessed by polymerase chain reaction were available for 12 children who completed a median period of seven months on ART. In 11 of these children, HIV-RNA was below detectable levels (<400copies/mL). Of these, eight children were ARV naïve, of whom five were prescribed AZT/3TC/NVP while three had AZT/3TC/EFV. Three children were ARV experienced (had received dual or mono ARV therapy) and were placed on D4T/DDI/NFV.

In one ARV-experienced child, a first-line ARV regimen was wrongly prescribed as the care-giver did not reveal this history. HIV-RNA levels in this child were at 54,000 copies at six months. The child was later changed to a second-line regimen.

There were six children who weighed 12–13 kg, two of whom received half a tablet (100 mg) of NVP twice daily (a relative underdose). All these children achieved HIV-RNA results below limits of detection.

Discussion

Scaling-up of ARV treatment in resource-poor settings will require decentralization and management by non-specialist doctors who often have a high-patient load and are unlikely to have had prior experience with prescribing ARVs in children. Introducing a standardized drug dosage table helped to alleviate some of the practical difficulties associated with prescribing ARVs for children in Thailand. Our experience with such a table has been encouraging for a number of reasons.

First, the great majority of doctors began to feel much more confident with prescribing ARVs in children and found the table practical, helpful and convenient. Many of these individuals made laminated pocket versions on their own, which they carried around and referred to during clinic sessions and ward-rounds. The table also became quickly visible on the desks and walls of consultation rooms within the different district hospitals.

Remarkable interest was also shown during National seminars and workshops and 1500 copies were sent on request by post to non-governmental organizations as well as individual clinicians countrywide. Based on the positive feed-back from its use, the Ministry of Health in 2002 incorporated an adapted version of the drug dosage table within the newest National Antiretroviral guidelines.[5]

Second, GPs in district hospitals in Thailand are often responsible for 100–200 out-patient consultations daily, while also being on call for the wards, for the emergency and delivery rooms. A standard dosage table avoids the need for calculations and thus saves precious time for the clinician who has a high patient load. It also reduces the risk of miscalculations. There is also the added advantage that any member of the team of clinicians, pharmacists, nurses and social workers can cross-check a given prescription with a glance at the dosage table and verify that the patient has been given the correct amount of a particular drug.

Third, preparing and dispensing drugs became easier for the caretaker as clinicians now took into consideration realistic divisions of available formulations of tablets.

Finally, the table is safe to use under routine conditions, judging from the low incidence of adverse side-effects. This is particularly true with the most commonly used ARVs. Preliminary evidence of viral suppression in the albeit small number of children who completed a median period of seven months of treatment was also

satisfactory and this is reassuring in terms of efficacy of the doses included in the table.

Although these preliminary findings related to safety and response are encouraging, this was an operational study carried out under routine programme conditions. Thus, we did not have a control group which could be included for comparison on children treated without the help of the table and using the same drug regimens. Historical data from Thailand are simply not available since this is the pioneering experience using HAART in such a setting.

Our main concern was the unavoidable limitation of the drug dosage table that is linked to its simplification. Fine-tuned or accurate dosing based on 'exact body weight' is not possible as all individuals in a specific weight range receive a fixed dose of drug(s) which may thus appear over- or under-dosed and could have a potential effect on the degree of viral suppression. One of the main 'yard sticks' for measuring satisfactory treatment response remains the suppression of viral load to undetectable levels. We wanted to be sure that, in our cohort, this was being achieved while using the recommended drug doses in the standardized dosage table. Our preliminary evidence shows that undetectable levels (<400 copies/mL) of virus were achieved in all of the five children who were ARV naïve and in 11 (92%) of the 12 children who had completed seven months of follow-up. This in its own right is reassuring in terms of treatment efficacy and virological suppression when compared with studies conducted under research settings.

Virological response rates in children are known to be inferior to those in adults when one considers the evidence from the limited numbers of published studies conducted on albeit small numbers of children.[11] Two previously published studies using the D4T/3TC/NVP regimen showed that in eight and two children, respectively, virological responses varied from 25% (<400 copies/mL)[12] to 50% (<50 copies/μL)[13] at six months of follow-up. The virological response rates[13] in children treated with a combination of nelfinavir and two NRTIs in 16 children varied from 69% (<400 copies/mL) and 44% (<50 copies/mL) at 12 months of follow-up.[14]

The issue of trying to achieve accurate dosing in countries with poor resources even while not using a drug dosage table is anyway not going to be realistic as long as syrups remain inaccessible and tablets and capsules remain restricted to available adult formulations.

Increasing the availability of more paediatric drug formulations is likely to enhance simplification of ART, which is in turn likely to be associated with improved adherence.[15,16] Despite the importance of this issue, large multi-national pharmaceutical companies that have a monopoly on the manufacture of ARV drugs consider developing countries a poor market for their drugs. Development of more adapted drug formulations for children is thus not a priority. There have also been very limited numbers of research studies carried out to assess ART drug dosages in children. This is particularly the case for boosted protease inhibitors. There is thus an urgent need for international advocacy on both of these issues.

In Thailand, the Ministry of health (MOH) and the GPO have became aware of the fact that the lack of paediatric formulations is an important barrier to implementing ART in children. The discussions between the MOH, the GPO and the different partners on trying to produce a standardized drug dosage table catalysed this awareness. The production of scored tablets and some paediatric formulations by the GPO were positive spin-offs of this realization.

The GPO now produces generic syrups and powders, some of which are 10–30 times cheaper than the brand name formulations.[17] Generic ARVs currently manufactured by the GPO include AZT (10 mg/mL), DDI – 30 and 60 mg, 3TC – 10 mg/mL, 3TC scored tablets – 150 mg, D4T capsules – 15 and 20 mg, D4T – 1 and 5 mg/mL, and NVP – 200 mg and NVP syrup – 10 mg/mL. Development of a higher concentration (5 mg/mL) of D4T syrup has been done to reduce the total volume of syrup that children have to swallow. The GPO is also developing a fixed-dose combination of AZT (10 mg/mL) and 3TC (6 mg/mL) syrup as well as 3TC (30 mg), D4T (7 mg) and NVP (50 mg) syrup to facilitate administration and adherence in children.

In resource-poor settings where paediatric drug formulations are not accessible and where health providers have little or no experience with ARVs, our preliminary experience with a standardized drug dosage table is that it provides a useful and safe tool to facilitate prescriptions for children.

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