Acceptability of Lopinavir/r Minitabs (Pellets), Tablets and Syrups in HIV-Infected Children

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1. ABSTRACT

Background: LPV/r 'minitabs' ("pellets") provided similar exposure to LPV/r syrup in the CHAPAS-2 trial. After 12 weeks, they were more acceptable than syrups for young children, but older children preferred tablets. Here we describe acceptability at week 48.
Methods: CHAPAS-2 was a randomised, 2-period crossover trial in HIV-infected infants/children taking first- or second-line ART with 2 NRTIs+LPV/r from 2 clinics ("JCRC", "PIDC") in Uganda. Infants aged 3-<12 months (group A, n=19) started syrup and switched at week 4 to minitabs; children aged 1-4 years (group B, n=26) started minitabs and switched to syrup or vice versa; and children aged 4-<13 years (group C, n=32) started tablets and switched to minitabs or vice versa. At week 8, all groups chose which formulation to continue. Formulation acceptability data were collected at weeks 4, 8, 12, and 48. VL was measured at week 48.
Results: For groups A and B overall, the proportion preferring minitabs increased between weeks 0 and 12 and decreased at week 48 (group A 37%, 72%, 44%; group B 12%, 64% and 36% respectively). However at week 48, group B's preferences differed between JCRC and PIDC: 70% JCRC vs 13% PIDC preferred minitabs. For older children (group C), minitabs were progressively less preferred to tablets over time: 41%, 19%, 13% at weeks 0, 12, 48 respectively.
Formulations taken in the preceding 4 weeks reflected preferences; clinics differed: groups A/B at JCRC more likely to be on minitabs at week 48 (40%/82% JCRC vs 15%/20% PIDC respectively). For group C, 23% and 13% were on minitabs at weeks 12 and 48 respectively.
Unpleasant taste was similarly reported among young children taking minitabs and syrups (37%/43% group A and 29%/26% group B), whereas among older children, minitabs were worse than tablets (40%/2%). There were no reported problems with storage and transportation for minitabs (0%/0% respectively) unlike syrups (23%/13%). Of 19 children with VL assayed at week 48, 14 were <50 c/ml and all were <1000 c/ml.
Conclusions: For infants and young children, minitabs were more acceptable at week 12 but not at week 48. Differences between clinics could reflect bias among healthcare workers for different formulations. Minitabs taste similar to the syrup, are easier to store and transport than syrup bottles, and represent an alternative formulation for young children unable to swallow tablets. Improvements in taste of the current formulation may help sustain acceptability.

2. INTRODUCTION

- Guidelines recommend a protease inhibitor (ritonavir boosted lopinavir (LPV/r)) for first- and second-line antiretroviral therapy (ART) in younger and older HIV-infected children, respectively[1].
- Access to second-line ART is increasing, but remains low (<4%) in resource-limited settings. Limited experience (especially in African infants and children) and lack of availability of affordable and appropriate paediatric formulations has restricted roll-out[2].
- Current LPV/r paediatric formulations are expensive; tablets are large and must not be crushed/split; syrups have an unpleasant taste and require refrigeration[3] and are used relatively infrequently (~15,000 infants and children in 2013 (WHO Global Price Reporting Mechanism))
- We previously reported that LPV/r exposure from a **minitab sprinkle formulation stored in capsules (hereafter referred to as "pellet")** was comparable with syrup, but lower than tablets, with no significant differences in subtherapeutic concentrations[4]. In the first 12 weeks of the study, pellets were more acceptable than syrups for younger children, but older children preferred tablets.
- In this study we evaluated acceptability of pellets compared to syrup and tablets up to week 48.

3. METHODS

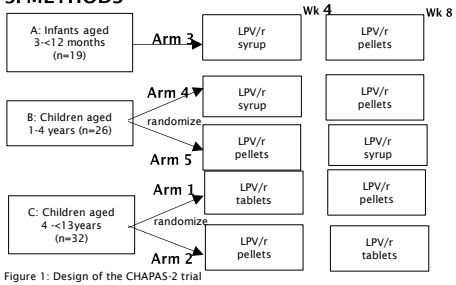


Figure 1: Design of the CHAPAS-2 trial

- 77 children were recruited from two clinics in Kampala: the Joint Clinical Research Centre (JCRC); and the Paed. Infectious Disease Clinic (PIDC)
- Children were allocate/randomised as in Figure 1. Carers then chose which formulation to continue from week 8 to week 48 (final follow-up).
- Acceptability data were collected at weeks 4, 8, 12 and 48.
- Viral load was measured at week 48.

4. RESULTS

4.1 Parent preference for pellets

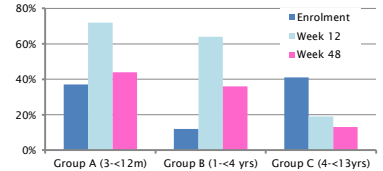


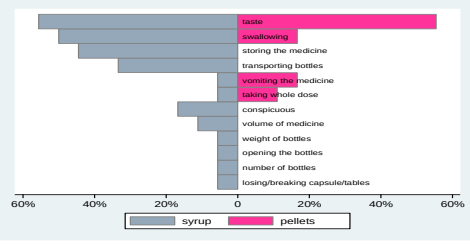
Figure 2: Proportion of parents preferring pellets by group and follow-up period

•For Groups A & B, the proportion of parents preferring pellets increased between enrolment and week 12 and decreased thereafter
•For Group B at week 48, 70% of patients at JCRC preferred pellets compared to 13% at PIDC
•For Group C, preference for pellets fell over the follow-up period

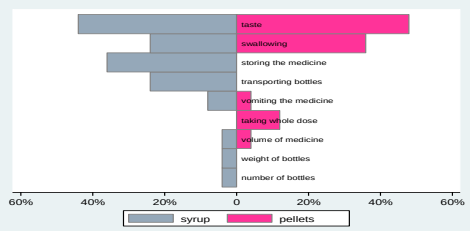
4.2 Problems with formulations during follow-up

Figure 3: Percentage of carers reporting problems with different formulations at any point during follow-up to 48 weeks

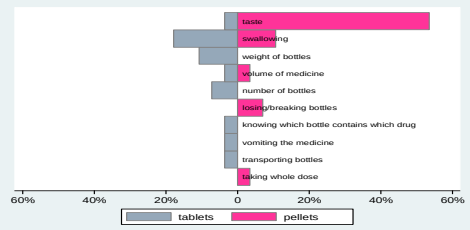
A: Group A (pellets vs syrup in infants 3 to <12 months)



B: Group B (pellets vs syrup in children 1 to <4 years)



C: Group C (pellets vs tablet in children 4 to <13 years)



- In groups A and B, the proportion reporting unpleasant taste was similar for syrup and pellets, while for group C pellets were worse than tablets
- No problems were reported with transporting/storing pellets, unlike syrups
- For those preferring syrups, key issues with pellets were their bitter taste, problems with masking this taste with food and needing to sweeten food with sugar or honey (which is expensive), and problems with giving the whole dose

4.3 Pellet use in the previous 4 weeks

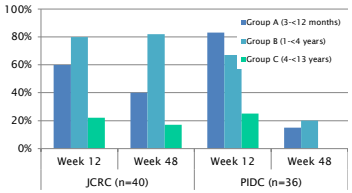


Figure 4: Proportion of children taking pellets in previous 4 weeks by group, time point and clinic

- The proportion of children taking pellets in the last 4 weeks reflected parent preferences, and differed by clinic. Generally, the proportion declined with follow-up period. Also, children at JCRC were more likely to be on pellets at week 48 compared to children at PIDC

4.4 Virological response

- Of 19/77 (25%) children with viral load assayed at week 48, 14 were <50c/ml and all were <1000c/ml

5. CONCLUSIONS

- For infants and young children overall, pellets were more acceptable than syrups at week 12 but not at week 48
- Higher pellet use at JCRC compared to PIDC at week 48 could reflect bias among healthcare workers for different formulations
- The taste of pellets is similar to syrup, and they are easier to store and transport than syrup bottles, and represent an alternative formulation for young children unable to swallow tablets
- Improvements in taste of the current formulation may help sustain acceptability.
- When pellets become licensed, healthcare professionals will need to support care givers to use them optimally

REFERENCES 1. http://www.who.int/hiv/pub/guidelines/arv2013/download/en/. World Health Organization (WHO). Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva; WHO, 2013. 2. Global HIV/AIDS response, Academic update and health sector progress towards Universal Access, progress report 2011; 3. EMA, Kaletra oral solution, SmPC. 4. Musiime V et al. JAIDS 2014; 66(2): 148-154.
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