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Acceptability of a new 4-in-1 Abacavir/Lamivudine/Lopinavir/Ritonavir paediatric fixed-dose combination: the caregiver–child dyads' perspective

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Abstract

Background: Worldwide, 1.7 million children younger than 15 years were living with HIV in 2021. Only 52% of them had access to antiretrovirals (ARVs). Lack of age-appropriate ARV formulations (i.e. easy to swallow for young infants, acceptable taste) remains the main obstacle to the access to ARVs. Therefore, a strawberry-flavoured Abacavir/Lamivudine/Lopinavir/Ritonavir (30/15/40/10 mg) fixed-dose combination of granules in a capsule (4-in-1) for children living with HIV weighing 3–25 kg was developed.

Objective: We assessed caregivers' perceived acceptability of the 4-in-1 compared with previous paediatric ARV formulations and factors influencing acceptability.

Methods: This exploratory qualitative case study embedded in a phase I/II, open-label, randomized cross-over pharmacokinetic, safety and acceptability study (LOLIPOP) was conducted in three sites in Uganda (May 2019–October 2020). Thirty-six children weighing between 3 and 19.9 kg participated in the main study. We purposively sampled caregiver–child dyads according to weight bands, and conducted 20 semi-structured interviews with caregivers and 5 with healthcare providers. We triangulated these results with a quantitative acceptability questionnaire. We analysed interviews inductively using NVivo12 adopting a thematic analysis approach and acceptability questionnaires descriptively to assess concordance between them.

Results: All caregivers found the 4-in-1 formulation highly acceptable and easier to use than previous formulations (i.e. pellets/tables/syrup). Appealing taste, ease of administration, easy storage and children's acceptance contributed to acceptability despite structural challenges of food shortage and HIV stigma. Visible improvements in children's health and comprehensive and tailored healthcare provider support to overcome initial difficulties such as vomiting increased caregivers' acceptance. Concordant results from questionnaire- and interview-data confirmed high acceptability.

Conclusion: Caregivers of children in all weight bands in this sample found the 4-in-1 granules highly acceptable compared with the pellets/tablets combination. Healthcare providers' support to caregivers allowed for individual tailoring of drug administration despite challenges such as food shortage. This enabled short-term adherence. These findings informed further practical recommendations.

Registration: Clinical trial number: NCT03836833

Keywords: acceptability, antiretroviral therapy, fixed-dose combination, HIV, paediatric ARV

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Introduction

Children living with HIV continue to be left behind by the global AIDS response. Globally, only 52% (800,000) of the 1.7 million children living with HIV aged 0–14 years in 2021 were diagnosed and on treatment, compared with 76% of adults.[1] Much progress has been made in the field of paediatric antiretroviral treatment (ART), but major treatment gaps persist.[2] Lack of age-appropriate ART formulations that infants and children can easily swallow, have an acceptable taste and are easy to store remains the main obstacles to ART access.[3,4]

Paediatric ART adherence levels vary from 49% to 100% in low- and middle-income countries (LMICs).[5,6] This wide range can be partly attributed to socio-cultural contextual influences and partly to the lack of standardized tools to assess paediatric adherence. Consequently, viral suppression in children is often poor as evidenced by pool analysis of 10 countries where only 37% of children are virally suppressed.[7] In addition, many acceptability studies of paediatric formulations, often seen as a precursor of adherence, have not been published.[8] While the precise contribution of acceptability to adherence is difficult to establish,[8] it is generally assumed that both user and product characteristics drive acceptability.[9] Research has demonstrated that multi-level factors beyond the characteristic of the medication itself influence acceptability, uptake and subsequently adherence. In addition to caregiver-related factors, studies demonstrated that structural factors such as poverty and food insecurity,[10] and health-systems related factors, for example, lack of comprehensive health services and limited access to health facilities,[11] were common challenges for paediatric HIV treatment in LMICs.[12] From a socio-ecological perspective, these factors act on and cut across different levels (i.e. the intra-individual, caregiver/family-, community-, healthcare provider (HCP)- and policy-level factors).[13] Implementation research to understand how health innovations, such as a new formulation, can be put into practice, has emphasized the importance to identify the multi-level constructs decisive for implementation success. To measure the impact of such constructs on implementation outcomes, Chaudoir *et al.*[14] developed a multi-level conceptual framework in line with a socio-ecological approach. Getting insights into these multi-level factors is relevant for the upscaling of the treatment, as lack of acceptability has been shown to be important for both implementation and health outcomes.[15,16] This makes it critical to understand how caregivers perceive a newly available paediatric HIV treatment formulation, such as the 4-in-1 formulation. This formulation, developed by Cipla Ltd. and Drugs for Neglected Diseases initiative (DNDi), is a strawberry-flavoured Abacavir/Lamivudine/Lopinavir/Ritonavir (30/15/40/10 mg) fixed-dose combination of granules in a capsule for HIV-infected children weighing 3–25 kg, also referred to as '4-in-1', that can be taken with liquids or semi-solid food.

The objective of this study was to explore caregivers' perceived acceptability of the 4-in-1 formulation compared with standard of care with Lopinavir/Ritonavir (LPV/r) (40/10 mg) pellets plus dual Abacavir/Lamivudine (ABC/3TC) (60/30 mg) dispersible tablets and other previously used paediatric ART formulations. In addition, we aimed to get insight into factors that may potentially influence caregivers' and children's acceptability of the 4-in-1 formulation. Based on these findings, we develop practical recommendations for future implementation.

Methods

Study context and design

This exploratory, qualitative case study was embedded in the phase I/II, open-label, randomized cross-over pharmacokinetic, safety and acceptability study (LOLIPOP) of the Abacavir/Lamivudine/Lopinavir/Ritonavir – 30/15/40/10 mg (4-in-1) fixed-dose combination *versus* LPV/*r* (40/10 mg) pellets plus dual ABC/3TC (60/30 mg) tablets (Figure 1). The unit of analysis was the caregiver–child dyad considered as cases. We collected qualitative data at three sites in Uganda: Joint Clinical Research Centre (JCRC), Baylor Uganda clinical centre of excellence and Epicentre Mbarara. This provided for potential contrasts and ensured that both urban and rural areas were included.

Sampling and data collection

Qualitative data collection. We adopted semi-structured interviews, allowing the collection of data in a structured and comparable manner, while ensuring flexibility to identify new areas and exploration of emerging topics more in-depth.

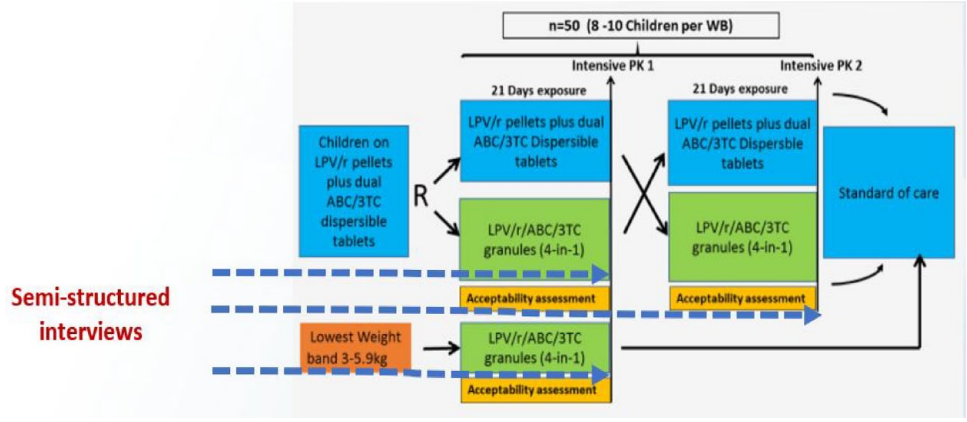

Figure 1. LOLIPOP study design and timing of semi-structured interviews and quantitative acceptability questionnaires.

Caregivers were sampled purposively according to the four World Health Organization (WHO) weight bands (WBs) (i.e. WB1: 3 to ⩽ 5.9 kg; WB2: 6.0 to ⩽ 9.9 kg; WB3: 10.0 to ⩽ 13.9 kg; WB4: 14.0 to ⩽ 19.9 kg) to capture a variety of experiences with the 4-in-1 formulation until data saturation was reached. For the current study, we adapted a topic guide from a previous study on acceptability of LPV/r pellets[13] (Supplemental Additional file 1). The adapted tool focused on personal experiences with the new 4-in-1 formulation, barriers and facilitators to treatment initiation, understanding of instructions received, coping strategies and routines developed to administer the 4-in-1, children's reactions, short-term adherence, perceived support strategies and comparison with the LPV/r pellets and ABC/3TC dispersible tablets formulation. We conducted the interviews during participants' hospitalization for the pharmacokinetic assessment, according to their randomization either on days 21–23, or at the end of the study, on days 42–44. For children between 3 and 5.9 kg (WB1), interviews were done on days 21, 22 or 23 (Figure 1).

We also conducted semi-structured interviews with HCPs, namely, nurses, to gain insights into their experiences and triangulate them with caregivers' perspectives. HCPs were selected during the study based on their interaction with study participants and their caregivers. The topic guide comprised comparable questions, including personal experiences with instructing caregivers in administering the new formula, personal perceptions of uptake, adherence support, provider–patient relationships, communication skills and observed challenges among caregivers with administration of the new formula. For the latter, we put emphasis on specific challenges with the lowest WB 3–5.9 kg (Supplemental Additional file 2).

The interview guides were pilot-tested in the study site Baylor college (Uganda) during February 2019 before trial initiation. Respondents were two caregivers and one nurse. All pilot participants provided informed consent but were not included in the qualitative assessment.

A Ugandan, male, trained social scientist (C.O.) working for the Makerere University with experience in qualitative research conducted the interviews in either English or in a local language (i.e. Kirundi, Rukiga, Runyankore or Luganda, based on interviewees' preferences) face-to-face at the health facilities in confidential spaces. There was no established relationship prior to study commencement between participants and the interviewer.

Study site personnel of the LOLIPOP trial approached caregivers of children who participated in the LOLIPOP trial and invited them personally to participate in an interview. If caregivers expressed willingness and interest, they received a participant information sheet with relevant study information. The interviewer personally invited HCPs to participate in the qualitative assessment. The interviewer obtained written informed consent from each caregiver and HCP prior to the start of the interview, and recorded the interviews upon agreement of the interviewee. Interview

duration varied between 30 and 40 min. The interviewer did not conduct repeat interviews, nor was data collected on refusal to participate. Study participants did not receive any incentives for their participation. Data were collected between 4 July 2019 and 6 October 2020.

Quantitative data collection. All caregivers filled in a quantitative questionnaire approximately 21 days after starting the 4-in-1 to assess short-term acceptability, mode and level of difficulty of administration by the caregivers, level of difficulty of intake by the children, frequency of drug refusal, spitting or vomiting, difficulties encountered by the caregiver and reasons for missed medications in the previous week (Figure 1).

Data analysis

Qualitative data analysis. The social scientist translated all recorded interviews into English while transcribing them verbatim from the local languages. During transcription, data were pseudonymized. We used an inductive coding process following a thematic analysis approach.[17] Two data analysts scrutinized the transcripts iteratively for emerging themes to develop a coding scheme using Nvivo12. The codes were then combined to relevant themes. The interdisciplinary study team identified common themes through a cross-case analysis and discussed discrepancies to achieve consensus.[18] In a second deductive step, we mapped the emerging themes onto the adapted framework of Chaudoir's *multi-level framework for implementing health innovations* to conceptualize how the identified themes contributed to the acceptability outcomes.[14]

Quantitative analysis and data source triangulation. We triangulated the results from the interviews with the findings from the acceptability questionnaires to enhance validity. We analysed the quantitative data descriptively to assess concordance between the two data sources. In addition, we performed a data source triangulation using findings from both semi-structured interviews with caregivers and HCPs to increase trustworthiness of the qualitative findings.

Ethical considerations

We obtained ethical approval for the study protocol including the qualitative assessment from the Institutional Review Board at the Institute of Tropical Medicine, Antwerp, Belgium (1264/18), and from the Ethics Committee of JCRC (JC2118) and the Uganda National Council for Science and Technology for all sites of the LOLIPOP study (JC2118).

Results

Participant characteristics

In total, we included 20 caregiver–child dyads. Caregivers' age ranged from 20 to 63 years. They were all children's primary caregivers, including biological mothers ($n = 17$), two grandmothers and one foster parent. Twelve caregivers had a secondary education level or higher and 13 were employed. The children were distributed over the different WBs as presented in Table 1 with an age range between 2.7 and 66.9 months. Eleven of the children were female.

All five HCPs were registered nurses; three were trained as paediatric nurses. Two were from Baylor Uganda, two from Epicentre and one from JCRC.

Caregiver–child dyads' perceived acceptability of the 4-in-1

Overall, caregivers found the 4-in-1 highly acceptable. They reported better experiences with the 4-in-1 compared with previously used paediatric ART formulations such as pellets. This was irrespective of their children's WB category. Caregivers also reported that their children easily took the new formulation.

> I don't have any problem with this new drug. It works well for me and my child compared to the syrup and the pellets. (Mother, WB3)

We identified several factors situated on different conceptual levels influencing acceptability and which we visualized in a conceptual multi-level framework[14,16] (Figure 2). They are grouped and presented in the following categories: acceptability factors related to the formulation, HCP-level factors, caregiver-related factors, organizational-level factors and structural factors.

Acceptability factors related to the formulation

Taste. In general, caregivers reported that the 4-in-1 paediatric formulation had an appealing

Table 1. Number of semi-structured interviews with caregivers by weight band and by clinical site.

	JCRC	Baylor Uganda	Epicentre Mbarara	Total
Weight band 1 (3 to ⩽5.9 kg)	0	1	5	6
Weight band 2 (6.0 to ⩽9.9 kg)	1	1	2	4
Weight band 3 (10.0 to ⩽13.9 kg)	3	1	1	5
Weight band 4 (14.0 to ⩽19.9 kg)	0	4	1	5
Total	4	7	9	20

JCRC, Joint Clinical Research Centre.

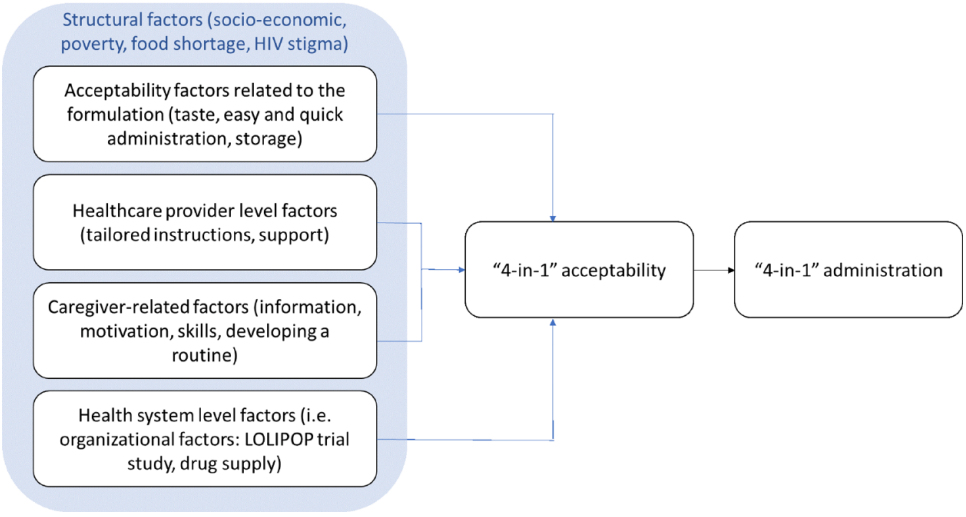

Figure 2. Conceptual multi-level framework.
Source: Adapted from Chaudoir *et al.*[14]; Wambiya *et al.*[16]

flavour and tasted sweet compared with previously used formulations, such as LPV/r pellets and syrup, which tasted rather bitter or sour. They perceived this as a big improvement.

> What my daughter likes about it is the fact that the 4-in-1 medicine is sweet, at one point she does not realize that it is medicine, she calls it sugar. (Mother, WB3)

Ease of administering. Ways of administration. The qualitative accounts revealed details on how caregivers prepared the medication to administer it to their children. Main food or drinks used were porridge, milk and water. Mothers who exclusively breastfed used breastmilk. Overall, caregivers quickly developed their own administration techniques. Some caregivers poured the granules into drinking cups, others onto spoons, or mixed the powder in porridge.

> I pick the two capsules I was told to give; I open them and pour on a spoon then I mix with breastmilk and give to the baby to swallow. (Mother, WB1)

Swallowing the medication. Caregivers reported that they preferred the 4-in-1 over the other child ART formulations, as children had fewer problems

swallowing the medication. They noted that the children could easily swallow the 4-in-1 when it was sprinkled over food or taken with liquids.

> The new type of medicine does not take long because it is already in powder form, it is easier to swallow compared to the old ones. (Mother, WB2)

Quick administration. Caregivers were able to quickly administer the 4-in-1 formulation within a short time.

> She takes her drugs twice a day [. . .]. It usually takes her 2 to 3 minutes to take the drugs. (Caregiver, WB4)

Only children in the lowest WB usually needed a longer time, as they had more problems in swallowing the medication than older ones. Based on their observations, HCPs' accounts corroborated that for most caregivers administering the new drug was easy and quick due to the characteristics of the drug and its fixed-dose combination. All interviewed HCPs reported that they would recommend other HCPs to prescribe the 4-in-1 to children living with HIV.

> It is better and easier to administer by the caregivers or mothers, easier for the children to swallow, it dissolves easily in water or any other medium and regarding the taste it is much better, easier to give . . . easier to dissolve all-in-one capsule. (HCP)

However, some differences emerged in terms of ease of administration comparing the lowest WB with the other WBs. HCPs found the children from the lowest WB more susceptible to vomiting and easily regurgitating, especially for breastfed children. These young babies were only used to a sucking technique and thus giving the medication was challenging:

> Since they have not yet started eating or drinking, giving them this drug has been more difficult because they are used to breast feeding so it is hard for them to take.(HCP)

Packaging and storage. Overall, caregivers and HCPs saw the fixed-dose combination, and its easy storage as particular advantages of the new formulation.

Size of the packaging. While most caregivers and HCPs accepted the fixed-dose combination package well, some caregivers found it too big, preventing it from being discretely handled. However, both caregivers and HCPs appreciated that it came in one single package, easy to carry and conceal, if needed:

> [. . .] I like about it (4-in-1) that it is in only one tin, more tablets can be carried in the same container – yet the old drug had more tins which required one to keep moving with more tins in one bag; as a mother sometimes you do not want people to see these medicines. But concerning the new one you can take one tin and you are well sorted. (Mother, WB1)

Storage at room temperature. Caregivers, especially those with poor living conditions, appreciated that no fridge was needed for storing the 4-in-1.

> Another good thing is that it is stored at room temperature than the first antiretroviral syrup which required someone to find a fridge to keep it safely. (Mother, WB3)

Challenging aspects of the 4-in-1. Challenges mentioned included different forms of vomiting and difficulties with administering it with food, and food availability. The latter was both dependent on caregivers' economic situation and on children's age.

Spitting, regurgitating, vomiting. Some caregivers reported that their children had initial 'vomiting' (in local language, the term vomiting could also mean spitting and regurgitating). This happened in first place when starting with the 4-in-1 because of the new taste and the amount of granules to swallow for older children. Depending on the child's weight, the number of capsules needed to be administered per treatment dose increases.

> Before I used to give the child medicine with only water and she found it hard, but the nurses told me to give the child medicine with either milk, tea, because before that she used to vomit but when I changed to something sweet, she stopped vomiting. (Mother, WB4)

Data from the HCPs confirmed this:

> One of the challenges was vomiting during the first dose among the older children of 10 kg and above or feel nausea and gag unlike the little ones. (HCP)

Giving 4-in-1 with food. According to the study protocol, HCPs advised caregivers to administer the 4-in-1 with food and beverages such as milk, yoghurt and porridge. Some caregivers, especially those who experienced financial problems, struggled with finding sufficient food and developed specific coping strategies to overcome this challenge. Some caregivers of children above the weight of 10 kg therefore preferred to pour the drugs directly into children's mouths and then give milk or water afterwards:

> What makes it a little complicated is that sometimes it is hard to get food for my daughter to eat immediately after taking the medicine, due to the fact that I am currently unemployed, this makes following regulations difficult. (Mother, WB3)

Healthcare-related provider-level factors

HCPs were well aware of their important role in instructing the caregivers. They felt that the specific instructions regarding how and with what to administer the 4-in-1 were key in achieving good acceptability and short-term adherence. HCPs shared ways in which they supported and addressed caregivers' questions, and they felt that this was appreciated by the caregivers. Appropriate communication and establishing a trusting relationship between caregiver and HCP was critical to ensure caregivers could freely express themselves in case of forgotten doses, mistakes or questions regarding administration methods.

> The social worker always calls them almost every day, asking them how they have managed. Some of the issues are: I gave the drug a bit late because I went for a burial today, so I missed the first dose because; or, I had gone somewhere and when I came it was late and I had forgotten so I have given one dose in a day. They would tell us those challenges. (HCP)

Tailored administration instructions enabled caregivers to find most effective and individually adapted ways to administer the 4-in-1 in a sustainable and affordable way to overcome the observed struggles, such as initial vomiting or food shortage.

> We advised them on [food] options that were affordable based on economic status, for example after realizing that yoghurt is very expensive for some mothers that they could get plan B; for those children who do not take milk they were advised on different types of foods and we gave them a chance to select what they could afford – provided it could be among the categories of foods we wanted. (HCP)

Starting the children on this new medication and maintaining the treatment, thus moving from uptake to adherence, was a process. In the beginning, some caregivers experienced difficulties to adhere to the strict timing to administer the antiretrovirals (ARVs). Caregivers reported good short-term adherence and attributed this to the visible improvements in their children's health and to supportive follow-up by HCPs (e.g. phone counselling).

> During the first period I did not take it so seriously to provide the medication in time but when I returned to the health facility the health workers emphasized that giving her medication in time was very important that was after they told me that the child's health had deteriorated, I need to find a particular time to administer the drugs so I started to take time seriously. (Mother, WB2)

Caregiver-related factors influencing acceptability

Caregivers' knowledge and level of information. Most caregivers knew well how to administer the 4-in-1, after initial uncertainties about what to mix the formulation with. Due to clear instructions, caregivers solved these initial problems and soon knew how to administer the 4-in-1 correctly. However, other practical barriers, such as food shortage or simply forgetting from time to time, emerged. Thus, while knowledge could not always directly be translated into correct practice, most caregivers knew about the negative effects of not giving the ARVs on time and also what to do when they forget.

> Not adhering to the drugs, the child's soldiers reduce (leading to higher viral loads). (Mother, WB3)

Caregivers' motivation. Information and support given by the healthcare staff and other people, for example, in their home or neighbourhood, motivated caregivers to adhere to the proposed treatment schedule. Observed positive changes in children's health served as another important

motivator, for example, sores in the mouth disappeared, the child no longer had diarrhoea. This made caregivers hopeful again about the future perspectives of their children. They attributed their progress to this medication and were determined to continue giving the 4-in-1 to their children.

> I have seen a big difference, because my child was so sick and he was almost dying, but everyone is now surprised about his appearance due to the help of the medicine and you the doctors. So, when I realized the truth, I always follow the doctor's instructions. (Mother, WB4)

Caregivers' skills: creating a personal routine. Caregivers determined their own most convenient time for administering the medication to their children. This depended on the best match with day-to-day activities, such as their work or school, to develop personal routine. They mentioned strategies, such as looking at the watch or setting an alarm on their phones or the beginning of a TV show, to remind them to administer the medication on time:

> I keep looking at the watch, for instance if I give him the medicine in the morning, it helps me to ensure that he takes the dose in the evening; I make sure that I do not delay at work; by giving the medicine to the child in the morning and the evening helps because afternoon hours are a bit risky since I will be at work. (Grandmother, WB3)

Organizational-level factors

Organizational factors pertained to the trial setting of the LOLIPOP study. The study setting granted drug availability as well as detailed information on the study medicines, comprehensive counselling and support, and appropriate follow-up given by dedicated study staff. This motivated HCPs to perform their job.

> The fact that I am part of the team that is working hard to generate new information about the new drug, it makes me feel good and also interacting with different people beyond Uganda including the manufacturers, sharing knowledge and emails, getting immediate feedback on what requires to be corrected is good. (HCP)

Structural factors

HCPs were aware that caregivers' personal lower socio-economic circumstances might influence their ability to adhere to the given instructions:

> Those who come from far are economically low, so they end up using what they have. For example, there is a participant who came and told me she did not have breastmilk and she does not have money to buy it [milk] so I imagine at one point she will be forced to use water. (HCP)

Stigma at the community and household level was another factor emerging from the data that impacted on accessing social support. Experienced or anticipated HIV-related stigma prevented some caregivers from disclosing children's HIV status to family members, leaving the responsibility for the drug administration on their shoulders. While some interviewees had no problems to disclose to anyone, in other cases, caregivers had only one or few persons in the family to whom HIV had been disclosed to. These were mostly close family members.

> Her grandmother [my mother] helps me in taking care of my child. The rest of the family members do not have a clue on how to take care of my child. [. . .] but they even do not know the status. (Mother, WB3)

Validity check with results from acceptability questionnaires

In terms of easiness to administer the 4-in-1, all except one caregiver found it very easy ($n = 10$) or easy ($n = 9$). No difference regarding level of difficulty to administer the 4-in-1 could be observed from the questionnaire results of the caregivers interviewed between the lowest WB and the other WBs. However, among the six caregivers reporting difficulties in swallowing the 4-in-1 granules by their children, three caregivers were from WB1. The difficulties in swallowing experienced by these children from WB1 ranged from sometimes refusing ($n = 3$) to sometimes spitting ($n = 1$), vomiting ($n = 3$), choking ($n = 1$) or coughing ($n = 1$) the 4-in-1. Only one child from the other WBs experienced infrequent vomiting.

Four caregivers encountered difficulties with the 4-in-1 packaging, either the size of the capsules

were too big or the volume of granules to swallow was too high.

Questionnaire data also confirmed the different applied administration methods. Five children were breastfed, but only one of them was exclusively breastfed. This caregiver reported to use the expressed breastmilk to mix the 4-in-1 with and to pour the mixture into the mouth of the child. One other caregiver who was not exclusively breastfeeding, used either cow's milk or breastmilk to administer the 4-in-1. Two caregivers administered the 4-in-1 directly into the mouth. Others made use of porridge ($n = 6$), milk-porridge ($n = 3$), water ($n = 4$), cow's milk ($n = 2$), tea without milk ($n = 1$), infant formula ($n = 2$) or juice ($n = 1$).

Overall, we found high concordance between questionnaire data from primary caregivers and qualitative data from the semi-structured interviews confirming high acceptability.

Discussion

Our findings show that caregivers of children of all WBs well-accepted the 4-in-1, and that both caregivers and HCPs preferred it over the previously used pellets or other ART formulations. Overall, children tolerated the 4-in-1 well, except for initial problems with 'vomiting'. Some problems with administering the medication emerged also for the lowest WB infants who still had problems with swallowing as they were not yet used to food. These initially observed problems were overcome with tailored and practical support from the HCPs.

The findings of this qualitative study reveal the complexity of administering paediatric medication and – to a limited extent – short-term adherence, as demonstrated before.[19] Several factors situated on different conceptual levels (i.e. acceptability of the formulation, HCP, caregiver, organizational and structural levels) emerged from our data exerting influence on both caregivers' and HCPs' acceptability. For each area, specific recommendations can be given based on our findings. They may contribute to optimized treatment and comprehensive care for infants and children living with HIV, as recently called for by a new global alliance launched to end AIDS in children by 2030.[1]

In this study, acceptability was highly influenced by characteristics related to the 4-in-1.

A study on acceptability testing showed that (after)taste and duration of administration are, among others, critical acceptability factors of paediatric formulations.[20] The qualitative data demonstrated that the children well-accepted the sweet taste of the 4-in-1, facilitating quick and easy administration. Both caregivers and HCPs identified the appealing flavour as a clear advantage over the previous bitter-tasting formulations.[21]

Adverse effects, such as nausea, taste disturbances or reduced appetite, have been reported with all ARVs and are the main reason for discontinuing, switching or non-adherence.[22] Initial immediate reactions of children towards the medicines by 'vomiting' in our study were overcome through practical support provided by the HCPs. Importantly, no drop-outs or cases of non-adherence were observed throughout the study, potentially attributable to the formulation's acceptability.

We identified several provider-related factors clearly contributing to the high acceptability of the 4-in-1. Evidence that HCPs are a key group of professionals influencing acceptability of new drugs among caregivers and ultimately patients has been demonstrated in the CHAPAS 2 trials, where HCPs, unfamiliar with the medication to be tested (i.e. pellets), could have influenced caregivers to prefer liquid formulations.[23]

The 4-in-1 was well-accepted by HCPs and they recommended solutions to caregivers in case of administration challenges. However, these challenges are highly individual depending on the child's age, the family environment and support system. Therefore, a patient-centred approach taking into consideration caregivers' comprehensive needs was much appreciated by the caregivers. This is in line with the results of a detailed realist evaluation of paediatric HIV treatment in the form of pellets.[24] Tailored support has to be specific and practical, to overcome individual problems and initial struggle by caregivers to administer a new formulation. Research has shown that adherence support often suffers from poor communication and a lack of clear instructions on how to take medication or what to take

the medication with to make it palatable for children.[4,25] Hence, when introducing new paediatric HIV formulations as the 4-in-1 outside of a study context, there is need to educate HCPs regarding the medication (e.g. the formulation and correct administration), as well as improving their counselling and communication skills to deliver adequate, positive-minded, client-centred care.

A body of evidence shows that the three constructs, that is, information, motivation and behavioural skills, which also emerged in this study, directly and indirectly influence adherence, as stipulated by the information-motivation-behavioural skills model.[26] This model provides a solid theory-base for HIV prevention and has also been empirically validated for adherence interventions.[25] Health-literacy can be increased by giving tailored information, motivation can be increased by identifying individual goals and resources, and administration skills are modifiable, for example, increasing self-efficacy, giving clear instructions or demonstrations of correct administration. Such factors are of crucial importance in adverse contextual circumstances as in the case of food shortage. Many caregivers in our study expressed this challenge, which has been recognized as a common factor of HIV treatment success.[10] Therefore, integrating patient-centred care in service provision with tailored instructions and support to the specific context of the caregiver is essential to increase self-efficacy, motivation and skills and so subsequently acceptability and adherence of HIV medication.

Clearly, findings of this study embedded in a clinical trial setting are not comparable with or generalizable to real-life settings. The organizational and health-systems context determines the quality of a health innovation's implementation, interventions including new medications, practices and guidelines. Several factors could be thought of that are relevant, such as workload of nurses and counsellors to deliver adequate counselling and follow-up, as done in the study context; guidelines should be available to standardize the procedures and instructions to increase caregivers' health literacy and support the administration of the 4-in-1; and most important, consistent drug supply must be ensured. For counselling to be effective in empowering caregivers to better cope with structural barriers (e.g. food shortage, poverty), HCPs should give clear-cut, yet tailored and culturally appropriate instructions. Health policies should consider providing integrated services, such as combining paediatric and adult services to save on, for example, transport costs, as many caregivers are living with HIV. Finally, further research in non-trial settings should shed light on acceptability and potential adherence outcomes of the 4-in-1.

The above-mentioned facilitators of acceptability and administration are embedded in a specific socio-economic context with structural factors influencing factors at the other levels, as well as the outcome. Here, we identified mainly poverty leading to food shortage and HIV-related stigma at the household and community level as critical contextual factors. We have shown that they can be overcome by tailored support from HCPs to develop adequate coping strategies at the individual level; also, the formulation itself, as it can be administered in quite a discrete way, can mitigate the effects of HIV-related stigma. However, while HCPs can support caregivers in coping with such structural barriers, policy-making should aim at removing these structural barriers in the first place. Examples from the literature to enhance adherence to ART through addressing structural barriers in resource-constrained settings may include for instance working with local structures and associations, such as micro-credit organizations or community-based ART programmes.[27,28]

We acknowledge some study limitations. As with all self-reported data, results may be affected by the bias of self-reporting. Interviewees were LOLIPOP trial participants; therefore, a social desirability bias cannot be excluded leading to potential underreporting of problems. These biases were mitigated by using an independent and well-trained social science researcher, clearly identifying as being independent from the trial team. While the questions initially focused on acceptability compared with previously used LPV/r pellets, caregivers' narratives sometimes included also previous experiences with other solid and liquid forms thus widening the scope of comparison. A strength of this study is its in-depth exploration through interviewing a large part of the entire study population and collection of rich data on their subjective perceptions. We also used triangulation to increase the trustworthiness of the qualitative findings.

Conclusion

Based on the study findings, the new 4-in-1 formulation is highly acceptable from the caregiver–child dyads' perception and experiences. It has some unique advantages for settings in LMICs. It can contribute to good adherence resulting in HIV viral suppression, which leads to longer, healthier and productive lives. This entire process starts, however, with acceptability as a necessary condition for maintaining treatment.

Declarations

Ethics approval and consent to participate

This study obtained ethical approval from the Institutional Review Board at the Institute of Tropical Medicine, Antwerp, Belgium (1264/18), and from the Ethics Committee of JCRC (JC2118) and the Uganda National Council for Science and Technology for all sites of the LOLIPOP study (JC2118). Eligible participants provided consent by agreeing to participate, after having been informed about the study and its procedures.

Consent for publication

Not applicable.

Author contributions

Anke Rotsaert: Formal analysis; Writing – original draft; Writing – review & editing.

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Juliet Mwanga-Amumpaire: Investigation; Supervision; Writing – review & editing.

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Mariama Diallo: Formal analysis; Project administration; Supervision; Validation; Visualization; Writing – review & editing.

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Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials

The datasets generated during and/or analysed during the current study are not publicly available, but are available upon reasonable request and if approved by DNDi.

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