PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optimizing neonatal antiretroviral therapy using raltegravir: a qualitative analysis of healthcare workers and caregivers' perspectives
AUTHORS	Katirayi, Leila Stecker, Carl Andifasi, Precious Mushavi, Angela Tiwari, Pradisha Jakazi, Chioniso Maphosa, Talent Thorsen, Viva Murandu, Mildrate Gombakomba, Gladys Mungati, More Denoeud-Ndam, Lise Rivadeneira, Emilia Weber, Rachel Hrapcak, Susan

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Helena Rabie Institution and Country: Department of Paediatrics and Child Health, South Africa Competing interests: None
REVIEW RETURNED	18-Apr-2022

GENERAL COMMENTS	General lack of diagnosis and timely initiation of therapy is again highlighted by this study. This is the most important and very serious take away message. There is low initiation in general and only 27 of 59 infants got RAL – what happened to the other babies. To assess the success of RAL would be valuable. Methods Why did all sites not have any patient s attending, is there a difference between sites? Would the study not be "better " if the HCW and caregivers of infants on ART but not RAL was also interviewed Describe how the questionnaire was validated and how the translation was performed. Results Also a description of the following is needed for infants 1) Age of test 2) Age of ART started 3) Number of infants attending day 8 vs day 28 or both 4) Day of the maternal interview 5) Maternal data on duration of therapy and VL

	6) Describe if comments differed between the d8 and d28 7) Add information on the total number of dosing errors and if there where common factors For HCW Include data on total expertise in neonatal HIV prescription and if there is a perceived difference with previous regimes like those based on NVP that may also need dosing escalation Add comments on how dose error can be be avoided and how this situation can be improved

REVIEWER	Reviewer name: Dr. Janine Abramson Institution and Country: University of Nottingham School of Health Sciences, United Kingdom of Great Britain and Northern Ireland Competing interests: None
REVIEW RETURNED	25-Apr-2022

GENERAL COMMENTS	Thank you for the opportunity to review this paper regarding the hugely important area of antiretroviral therapy in neonates. I find that it is extremely easy to read and therefore understand, despite having little experience of this subject. I would like to also commend the use of direct quotes which help build a picture of the viewpoints of the health care workers and parents/caregivers. I just have a few comments and questions:- * a little clarification around participants and non-participants would be of value in the data collection section. Out of the 27 that are prescribed and initiated on RAL, only 15 parents/caregivers are interviewed. Does this relate to the fact that six sites were excluded due to incomplete dose regimens at that point in data collection? Can this be made more clear? * why was the data collection period only over one month? Is this due to the fact the interviews were completed a year after treatment, in an attempt to reduce recollection bias? If so, can this be made clear? Or a justification as to why the data collection period was only over a month. *I find the added inclusion of political issues around staffing in Zimbabwe healthcare institutions a little confusing and potentially unnecessary. I realise the lack of healthcare staff would impact the training in education and prescribing of RAL, but a simple paragraph with this as an issue would suffice rather than the detail given in the discussion. I find it detracts from the important messages that are being offered. * I also find the discussion around how training is completed a little distracting and confusing, again could it be simplified. *Why were only 27 babies initiated on RAL, when 59 are diagnosed with HIV? Can this be addressed in the discussion? *What is the concern with dissolving the RAL in breast milk? Does it affect the pharmacokinetics of the drug? Is this discussed in the training? How easy is it for the parents/caregivers to obtain fresh water easily and daily, to enable dissolution of the drug? Were the parents asked about this practicality in the interviews? Did parents comment on palatability or tolerability of the medication for their babies? * The potential shame and concern around the HIV stigma is discussed in relation to the parents/care givers. I wonder is this an issue with the Healthcare workers, is there any bias in prescribing this drug or accessibility to it influenced by healthcare workers views? Does this affect early access to the drug and are parents able to get support once they have been discharged home with the medication? * How is the cultural issues of stigma addressed? This would be of value in the discussion. Are healthcare workers trained in such issues? * I would suggest that the sample size is also a limitation. I understand that the number of interviews required to be representative of a group is a contentious and controversial issue,

	but, this is only representative of those parents/care givers who were compliant in the medication during the first year of implementation. And as you mention, views are also given retrospectively. This may hinder the ability to generalise study results to wider population in general, however, the finding do raise crucial points about the ability to deliver ART in future, and are valuable in considerations of implementation and training, which is suggested by the authors.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Helena Rabie **Comments to the Author** General lack of diagnosis and timely initiation of therapy is again highlighted by this study. This is the most important and very serious take away message. There is low initiation in general and only 27 of 59 infants got RAL – what happened to the other babies. To assess the success of RAL would be valuable. Response: Thank you for this important observation and comment. As part of this project, a separate quantitative study captured additional data on all 59 babies that provide further insight into the other babies. Due to the different methodology used and results from the quantitative study, including all of these methods and findings within this manuscript would not allow for adequate discussion of those important findings. Therefore, a separate manuscript is being developed to describe and discuss the quantitative study findings. Methods Why did all sites not have any patient s attending, is there a difference between sites? Response: Fourteen sites were identified to pilot implementation of RAL granules. However, over the time of project implementation, an average of two babies were started on RAL each month across the different sites. To achieve the sample size for this qualitative study to achieve saturation, not all caregivers of babies that had received RAL were included in this study. To minimize recall bias, the caregivers of babies who had most recently completed RAL were included in the qualitative study. This meant that not all of the 14 sites were represented in this study sample, as they may not have had babies who had recently completed a course of RAL granules. Babies who had been initiated on RAL but had not yet reached a requisite follow-up visit were excluded from participating, as they would not be able to respond to the questions. Although there may be some differences between characteristics of project sites, the fact that about half of babies that had received RAL and over half of the sites were included are re-assuring as for qualitative studies, large sample sizes are not needed to reach saturation. Would the study not be “better” if the HCW and caregivers of infants on ART but not RAL was also interviewed Response: Thank you for this suggestion. The objective of this qualitative study was to assess experiences and acceptability of RAL granules amongst healthcare providers who prescribed RAL granules and amongst caregivers who prepared and administered the RAL granules. Caregivers who did not prepare and administer RAL granules or healthcare workers who were not familiar with RAL granules would not be able to provide insight into the acceptability of the medication formulation, so were excluded from the study. Describe how the questionnaire was validated and how the translation was performed. Response: All data collection tools were pre-tested at health facilities not participating in the study. Questions were edited and adapted to ensure that the question was correctly conveyed and understood by potential participants. This information has been added to line 150-152. Audio-recordings were simultaneously transcribed and translated into English transcripts. We have added this information

to line 168. Please note that in Zimbabwe English is spoken widely, so simultaneous transcription/translation is routinely practiced. Results Also a description of the following is needed for infants 1) Age of test: Response: We did not collect the date that the infant was tested for HIV. However, we did collect information about the number of weeks the infant had been on RAL. Babies eligible for RAL granules were diagnosed with HIV before two weeks of age, per national implementation guidance. We have added more information about the number of weeks each infant was on RAL into the demographics section, please see line 185-187. Specific data on the age of diagnosis for all babies was collected through the quantitative study, and will be reported in that manuscript. 2) Age of ART started: Response: Specific data on the age of ART initiation for all babies was collected through the quantitative study, and will be reported in that manuscript. Within this subset of babies included in the qualitative study, we do have the duration of time that the babies were on RAL and this has been added to the manuscript, (line 185-187). 3) Number of infants attending day 8 vs day 28 or both Response: We did not collect data regarding whether babies had attended the 8 day or 28 day appointment, rather we collected data regarding their length of time on ART, please see line 185-187. 4) Day of the maternal interview Response: The majority of caregiver interviews occurred in May 2021. Data were collected in July 2021. We have added additional information about the interview dates into the data collection section, please see line 157-160. 5) Maternal data on duration of therapy and VL: Response: We did not collect data on maternal treatment history and outcomes, as it was beyond the objective and scope of this study. 6) Describe if comments differed between the d8 and d28 Response: Data were not analyzed to determine differences between those who were interviewed after d8 compared to d28. The study did not intend to measure differences in perceptions towards RAL over time, but rather to understand the acceptability of the drug among caregivers in general. 7) Add information on the total number of dosing errors and if there where common factors For HCW Include data on total expertise in neonatal HIV prescription and if there is a perceived difference with previous regimes like those based on NVP that may also need dosing escalation Response: Although healthcare workers were asked in this study about their experience with changing RAL dosage and frequency at day 8, the number of dosing errors was not asked during the HCW interviews. Regarding expertise in neonatal HIV prescription, we did not capture data on this specific question. However, we did collect data on how long they have been in this position at this facility or other facilities and how many months they have been prescribing RAL granules. This information has been added to the manuscript to provide some context on the experience of the healthcare providers interviewed (see line 189-193). Healthcare workers did note that RAL was preferred over other available pediatric ART formulations, which we included in the manuscript; however, the comments around this were not related to dosing issues. Add comments on how dose error can be avoided and how this situation can be improved Response: We have provided suggestions in the results and discussion section on healthcare worker training recommendations. See line 388-390. Collecting data on the dosage prescribed by healthcare workers was beyond the scope of this study, and can be an area for future study using other more appropriate study methodology. Reviewer: 2 Dr. Janine Abramson, University of Nottingham School of Health Sciences **Comments to the Author** Thank you for the opportunity to review this paper regarding the hugely important area of antiretroviral therapy in neonates. I find that it is extremely easy to read and therefore understand, despite having little experience of this subject. I would like to also commend the use of direct quotes which help build a picture of the viewpoints of the health care workers and parents/caregivers. I just have a few comments and questions: * a little clarification around participants and non-participants would be of

value in the data collection section. Out of the 27 that are prescribed and initiated on RAL, only 15 parents/caregivers are interviewed. Does this relate to the fact that six sites were excluded due to incomplete dose regimens at that point in data collection? Can this be made more clear? Response: Fourteen sites were identified to pilot implementation of RAL granules. However, over the time of project implementation, an average of two babies were started on RAL each month across the different sites. To achieve the sample size for this qualitative study to achieve saturation (a situation in qualitative research in which data collection from additional participants does not yield any novel results), not all caregivers of babies that had received RAL were included in this study. To minimize recall bias, the caregivers of babies who had most recently completed RAL were included in the qualitative study. This meant that not all of the 14 sites were represented in this study sample, as they may not have had babies who had recently completed a course of RAL granules. Please see the additional text added on line 160-161. Babies who had been initiated on RAL but had not yet reached a requisite follow-up visit were excluded from participating, as they would not be able to respond to the questions. The fact that about half of babies that had received RAL and over half of the sites were included is re-assuring, as for qualitative studies, large sample sizes and representation from large proportions of the population are not needed to reach saturation. A reference is included in the manuscript that further describes saturation in qualitative research: Guest G, Bunce A, Johnson L. How many interviews are enough?: An experiment with data saturation and variability. Sage. 2006;18(1):59-82. https://doi.org/10.1177/1525822X05279903. * why was the data collection period only over one month? Is this due to the fact the interviews were completed a year after treatment, in an attempt to reduce recollection bias? If so, can this be made clear? Or a justification as to why the data collection period was only over a month. Response: Over the project time period, there were an average of two babies/month started on RAL granules. Therefore, it would take several months for enough babies to have started on RAL to achieve an appropriate sample size to reach saturation for this qualitative study. To maximize efficiency of staff time and study resources, data collection occurred over one month. In order to reduce the risk of recall bias, caregivers of babies who most recently administered RAL granules were included in this study. *I find the added inclusion of political issues around staffing in Zimbabwe healthcare institutions a little confusing and potentially unnecessary. I realize the lack of healthcare staff would impact the training in education and prescribing of RAL, but a simple paragraph with this as an issue would suffice rather than the detail given in the discussion. I find it detracts from the important messages that are being offered. Response: The structure of staffing in Zimbabwe (and most of Africa) has significant impacts on training staff. It is important to explain the challenges with the staff rotations to help inform implementing agencies and policy makers so that either the policies are changed or additional training is offered to ensure staff are well versed in the new drug regimens. This information is valuable for RAL and new public health guidelines. * I also find the discussion around how training is completed a little distracting and confusing, again could it be simplified. Response: We have clarified the language regarding how training is completed, please see the edits in line 388-390. *Why were only 27 babies initiated on RAL, when 59 are diagnosed with HIV? Can this be addressed in the discussion? Response: Thank you for this important observation and comment. As part of this project, a separate quantitative study captured additional data on all 59 babies that provide further insight into the other babies. Due to the different methodology used and results from the quantitative study, including all of these methods and findings within this manuscript would not allow for adequate discussion of those important findings. Therefore, a separate manuscript is being developed to describe and discuss the quantitative study findings.

*What is the concern with dissolving the RAL in breast milk? Does it affect the pharmacokinetics of the drug? Is this discussed in the training?? Response: The RAL granules do not dissolve as well in breastmilk or other liquids, which may impact the administration of the solution and absorption of the medication. RAL granules must be reconstituted in order to prepare the exact dose prescribed ie prepare granules in 10 mL of water then withdraw the appropriate dose. The pharmacokinetic studies to determine the strength and reconstitution instructions were conducted using water. As such, reconstituting with anything other than water cannot guarantee the 10ml solution of RAL has the appropriate concentration to then withdraw the prescribed dose from. *How easy is it for the parents/caregivers to obtain fresh water easily and daily, to enable dissolution of the drug? Were the parents asked about this practicality in the interviews? Response: In Zimbabwe, the urban areas generally have potable water. In rural areas, efforts have been made to provide potable water through boreholes. Caregivers were not asked about their ability to obtain clean water directly. However, caregivers were asked to report any challenges they experienced preparing RAL and challenges with accessibility to clean water was not raised. *Did parents comment on palatability or tolerability of the medication for their babies Response: The caregivers did not discuss any challenges with palatability or tolerability of the medication, but a few caregivers did report that being babies, they naturally sometimes spit up the medication. Caregivers did not necessarily report this as a concern, but more as a comment regarding their experience administering the medication. In our results, we included that healthcare workers noted the benefits of administering RAL in the granule form is that it is less bitter than other medications (line 245-247), making it more palatable for the babies. * The potential shame and concern around the HIV stigma is discussed in relation to the parents/care givers. I wonder is this an issue with the Healthcare workers, is there any bias in prescribing this drug or accessibility to it influenced by healthcare workers views? Does this affect early access to the drug and are parents able to get support once they have been discharged home with the medication? Response: Neither the caregiver or HCW interview guides directly asked about stigma, however, the caregivers raised the issue of stigma during their interviews, and therefore it is reported. No data regarding HCWs and stigma was reported. Previous literature does document differential treatment by HCWs towards HIV-positive patients, but stigma experienced by HCWs is not usually related to prescribing medications. Because stigma was not a focus of this paper, the discussion regarding stigma is limited. * How is the cultural issues of stigma addressed? This would be of value in the discussion. Are healthcare workers trained in such issues? Response: Because our study did not directly gather data on stigma, we feel that it is beyond the scope of the paper to discuss stigma in more depth. Also, the literature on stigma, and the many different types and levels of stigma is very rich, so we chose to focus the discussion on novel findings not previously described in the literature. * I would suggest that the sample size is also a limitation. I understand that the number of interviews required to be representative of a group is a contentious and controversial issue, but, this is only representative of those parents/care givers who were compliant in the medication during the first year of implementation. And as you mention, views are also given retrospectively. This may hinder the ability to generalize study results to wider population in general, however, the finding do raise crucial points about the ability to deliver ART in future, and are valuable in considerations of implementation and training, which is suggested by the authors. Response: Thank you for this comment. We do not attempt to generalize the results of the study to the wider population. The objective of qualitative studies is to gain a contextualized understanding of behaviors, beliefs and motivations, as opposed to quantitative research, which aims to quantify data and extrapolate the results to a broader population. For qualitative studies, large sample sizes

and representation from large proportions of the population are not needed to reach saturation (a situation in qualitative research in which data collection from additional participants does not yield any novel results). A reference is included in the manuscript that further describes saturation in qualitative research: Guest G, Bunce A, Johnson L. How many interviews are enough?: An experiment with data saturation and variability. Sage. 2006;18(1):59-82. https://doi.org/10.1177/1525822X05279903.

VERSION 2 – AUTHOR RESPONSE

Thank you for alerting our attention to these remaining challenges. We have removed the requested sentence regarding the 'first study,' shortened the discussion section, and updated 'what this study adds' as requested.

Thank you for your time and consideration of our manuscript.