PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A qualitative study of the BREATHER trial (Short Cycle antiretroviral therapy): is it acceptable to young people living with HIV?
AUTHORS	Bernays, Sarah; Paparini, Sara; Seeley, Janet; Namukwaya Kihika, Stella; Gibb, Diana; Rhodes, Tim

VERSION 1 - REVIEW

REVIEWER	Mette Frahm Olsen University of Copenhagen
REVIEW RETURNED	21-Jun-2016

GENERAL COMMENTS	Overall, this is a very well-written paper about a relevant substudy on patients' perspectives on short cycle ART, which was part of an RCT on this approach. However, I am not sure about the timing of this paper, since its relevance depends very much on the findings of the RCT - i.e. the perceptions and acceptability of this treatment approach may only be of interest if the RCT concludes that the approach is not associated with reductions in virological control. In addition, the authors describe that this paper reports only on data from the "first two waves" of interviews (p 6) and that additional data was collected on participants' views on dissemination of trial results and on potential roll-out of strategy (p 7). I think it would make a much stronger paper, if these data were combined in one paper to be published once the effects of SCT are known. I have listed additional comments below: p 4: I think the diversity of study settings is an additional strength of the study. It would be useful if the results section included a comparison of patients' perspectives in low- and high income settings. P 5: SCT seems like a relevant strategy, since it is my impression that it corresponds to how patients often take their ART (break on the weekends). It would add to the introduction, if relevant literature looking at this could be included. P 6: Specific objectives are not clearly described P 6: the methods are not well described. E.g. how often were "repeat" interviews done? What does it mean that data from the "first two waves" are reported? What does other waves focus on? What were the inclusion criteria in the trial? P 7: decription of data analysis should be more detailed. E.g. how were codes assigned to data? How were themes applied, etc? P 7 – sample: it is very unclear why almost half of the sample was recruited from the CT arm of the study. These patients will not be able to contribute to the objective of exploring the experience of SCT. In general, results are described as if only relating to patients in the SCT arm.

	P 8: A description of the participants (mean age, time living with HIV, time on ART etc) is missing P 13: The subtitle “other young people and SCT” could be improved to “concerns for other young people” or similar. I think it is much more interesting to hear directly from patients how SCT worked for them than to hear how they think it may work for other patients. P 14: The summary of findings could only be based on participants from the SCT arm. P 15: I it not clear whether these participants were actually “explempary adherers” as stated here. It was actually described how they chose not to tell clinicians about missed doses. It would be relevant to include a discussion about why participants are giving this information to interviewers but not clinicians. Better rapport? Or are clinicians just not asking the right questions? P 15: “perceptions of themselves, health and HIV” seems quite vague/unfocused… P 16: “data in the quantitative adherence… the clinical database” this refers to data that have not been reported here? P 17: The conclusion uses some rather general terms, e.g. “so many participants” and “early adjustments”. It would be more useful if these issues were described so that readers were left with a better impression e.g. of how much time was usually needed for adaption. It is not clear if this is a few weeks or several months…

REVIEWER	Katerina Christopoulos University of California San Francisco USA Recipient of grant funding from the National Institutes of Health Scientific Advisory Board Member, Roche Community Advisory Board Member, Gilead
REVIEW RETURNED	30-Sep-2016

GENERAL COMMENTS	The submitted manuscript describes a qualitative sub-study of the BREATHER randomized clinical trial, which compared 5 days on/2 days off antiretroviral therapy to continuous antiretroviral therapy for youth aged 8-24 years. It is so refreshing to see qualitative work integrated into the conduct of this kind of trial and this well-written manuscript has the potential to make an important contribution to the literature. However, there are several issues that limit enthusiasm for the manuscript in its current form. As an overarching comment, I suggest that the authors review and address the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist, as it would be a systematic way to address many of the outstanding methodologic questions readers may have. Critical information is missing from the methods section, particularly with regard to the research team, data collection, and the coding process. Who conducted the interviews? Were interviewers known to the participants? Were they involved in the analysis? How long were the interviews and where did they take place? Were participants reimbursed for participation? How was the interview guide developed? Interviewing a 10-year-old is likely to be quite different from interviewing a 24-year-old. If there are standard techniques to maximize the success of qualitative work with children, the authors should describe what they are and whether these were employed.

	Who coded the data and what was the coding process? Were some codes determined a priori based on the interview guide? What was the concordance between coders? Can the authors report a kappa statistic? The authors describe the use of negative cases but no negative cases are presented in the results. Were there any participants in the SCT arm who preferred continuous therapy? We are told repeat interviews were conducted but not the criteria for how far apart they had to be or how far into trial participation the first interview could occur. Understanding the timing of the interviews helps interpret the results and would strengthen the conclusion in the abstract that support and education be provided for 3 months to allow adaptation. Also, did all 43 participants undergo repeat interviews? Or were interviews halted when saturation was achieved? Half of the sample is from Uganda, yet less than half of the Ugandan participants approached agreed to participate in the qualitative study. The authors should discuss whether: 1) there were differences between developed and developing world sites, and; 2) whether the Ugandan sample may be biased toward “compliers.” It would be helpful to know the age of the participant in addition to the country and trial arm. Were any differences observed by age? The initial concerns of participants and the adaptation period required are nicely described. Very nice information on how stable viral load can justify non-disclosure of adherence issues. I’m not sure the first two quotes with regard to side effects add anything; the last quote may be sufficient. The idea of SCT as progress and reward is important and intriguing but the quote provided does not entirely support the claim. Are there additional quotes? The authors appropriately acknowledge that the acceptability of SCT applies only to the trial population. In the Discussion, the authors mention that qualitative findings regarding adherence are different than data from quantitative surveys and adverse event reporting but the reader is not told what the quantitative findings and this comparison is not outlined in the background or methods. One obvious question is whether any participants in the continuous therapy arm self-interrupted treatment due to participation in the trial, that is, they crossed themselves over to the intervention arm. Thank you for the opportunity to review this manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name
Mette Frahm Olsen

Institution and Country
University of Copenhagen

Please state any competing interests or state 'None declared':
None Declared

Please leave your comments for the authors below
Overall, this is a very well-written paper about a relevant substudy on patients' perspectives on short cycle ART, which was part of an RCT on this approach. However, I am not sure about the timing of this paper, since its relevance depends very much on the findings of the RCT - i.e. the perceptions and acceptability of this treatment approach may only be of interest if the RCT concludes that the approach is not associated with reductions in virological control. In addition, the authors describe that this paper reports only on data from the "first two waves" of interviews (p 6) and that additional data was collected on participants' views on dissemination of trial results and on potential roll-out of strategy (p 7). I think it would make a much stronger paper, if these data were combined in one paper to be published once the effects of SCT are known.

Thank you for your review of the paper. We are pleased that you agree that this is a relevant study to more fully understand the impact of SCT by focusing on the perspectives of the young people involved in the trial. We would like to explain the reasons behind the timing that you identify. The original intention was for this qualitative study paper to be published alongside the trial paper in a twinned publication. This was not possible because firstly, there was a time lag between our paper being ready and the trial paper being ready for publication. The two papers were submitted together and the trial paper was accepted for publication. We feel that it was a great shame that the editors of that journal overlooked the significance of the qualitative evidence and the need for it to be published to provide an informed assessment of the acceptability of SCT to young people themselves, the target of this treatment regimen intervention. We are delighted that the editors of the BMJ Open are more open to the value of qualitative sub studies within RCTs, especially when the RCT is testing a behavioural intervention as in our case. We have responded to this issue which is critical to the discipline of public health by addressing this point briefly in the third paragraph of the discussion section.

Due to the delays described above we are now able to include all of our data within this revised paper. So the phase 3 interviews and the Focus Group discussions, referred to as ongoing in the earlier version of this manuscript, are now presented and discussed. Our revised paper is longer as a result, but is stronger for the inclusion as we are able to reflect on young people's views now that the effects of SCT within the trial are known.

I have listed additional comments below:

p 4: I think the diversity of study settings is an additional strength of the study. It would be useful if the results section included a comparison of patients' perspectives in low- and high income settings.

We describe on pages 10, 12 and 13 that there were no notable differences in patients' perspectives in low and high income settings. For emphasis we have added a sentence on page 12 stating that despite analysing for differences there was a surprising commonality between accounts across all

settings and that any slight differences pertained to the style of accounting, which meant that accounts differed slightly across setting and across the sample age range but not in content.

As outlined on page 10 the primary difference between the sites was that in the UK recruitment was more difficult with higher levels of refusals, whereas in the USA and Ugandan sites there were virtually no refusals amongst those invited to participate in the qualitative study. We note that in the UK recruitment was challenging both into the trial and then amongst those eligible to participate in the qualitative study. Although we were unable to collect data on this, our impression is that this reflects a potential research fatigue given the extent of research conducted with this relatively small clinical population.

P 5: SCT seems like a relevant strategy, since it is my impression that it corresponds to how patients often take their ART (break on the weekends). It would add to the introduction, if relevant literature looking at this could be included.

There is no specific published evidence which indicates that SCT is definitively a relevant strategy for young people living with HIV, however there is considerable anecdotal evidence available which informed much of the impetus for designing an intervention in which the short treatment interruption would be scheduled over the weekends. This point has been added on page 7.

This is indicative of a lack of empirical evidence about how young people actually take their HIV treatment. We have a paper in press which examines how young people comply more strongly to a script of near perfect adherence rather than taking treatment exactly as prescribed. We have included this reference to our own paper in the introduction. We would welcome any suggestions for literature that we may have missed which presents evidence for young people taking weekends off.

P 6: Specific objectives are not clearly described
Thank you for this suggestion. We have included on page 8 the primary objective of the sub study, which was to assess the acceptability of this intervention to the target patient group and to inform any future roll-out.

P 6: the methods are not well described. E.g. how often were “repeat” interviews done? What does it mean that data from the “first two waves” are reported? What does other waves focus on? What were the inclusion criteria in the trial?
The methods section has been revised and expanded to more clearly explain our approach. The study design employed repeat interviews with the same sample group. The first interview, conducted towards the start of the trial (Uganda, UK and USA) explored attitudes towards taking HIV treatment and how doing so fit in, or not, with their daily lives and priorities. The second interview, conducted at least 9 months into the trial (Uganda, UK and USA), focused on their experience of being in the trial, including SCT. The third interview, conducted towards the end of the trial and/ or as they moved into the follow-up stage of the trial (Uganda and UK), looked at their ongoing experience of the trial and their preferences for future treatment options. The focus group discussions (FGDs) were only conducted in Uganda and done after the trial findings had been explained to participants. We include details on the FGDs sample on page 12.

The inclusion criteria of the trial have been reported on page 8. We have added the trial reference for further details.

P 7: decription of data analysis should be more detailed. E.g. how were codes assigned to data? How were themes applied, etc?
We have added more detail on this on page 9.

P 7 – sample: it is very unclear why almost half of the sample was recruited from the CT arm of the study. These patients will not be able to contribute to the objective of exploring the experience of SCT. In general, results are described as if only relating to patients in the SCT arm.

The inclusion of those in the CT arm of the study as well as the SCT arm was fundamental to our ability to meet our primary objective which was to explore the acceptability of SCT to the target patient group. Now that we have explicitly stated our objective we hope that this is clearer. We are interested not only in the experiences of those experiencing the weekend breaks, but the attitudes of those on continuous therapy and whether and why they feel that it would be beneficial to them. They had all contemplated the idea that they may be randomised to SCT and so had important insights to share that help us understand how such an intervention might be perceived by others within this clinical population. We now include an explicit explanation about this on pages 11 & 12.

We report results from both arms, but also with the inclusion of additional data there are additional extracts from those on the CT arm.

P 8: A description of the participants (mean age, time living with HIV, time on ART etc) is missing
We have added further detail into the overview of the sample in each site in the table on page 11.

P 13: The subtitle “other young people and SCT” could be improved to “concerns for other young people” or similar. I think it is much more interesting to hear directly from patients how SCT worked for them than to hear how they think it may work for other patients.
We have edited this so that it instead reflects the young people’s responses to the trial findings, which includes their concerns for other young people amongst other considerations.

We do think that it is necessary to reflect on how those in the trial think that it may work for other patients as part of our objective was to consider how their experiences and perspectives might inform any future roll-out. This is because in reflecting on their own adherence experiences it matters what their own relationship to adherence is. A weakness of the trial and the qualitative sub study is that we are only considering the effect of SCT on those who have an undetectable viral load. Given that we are learning through the qualitative study that some participants would describe themselves as not being exemplary adherers (discussed further on) it is useful to note how they have struggled with the idea of SCT and how they think others who have more problematic non-compliance would view it. This is especially important given that they are all concerned that for some young people the option of SCT might worsen rather than improve their adherence.

P 14: The summary of findings could only be based on participants from the SCT arm.
We have amended our findings to provide a more balanced distribution of extracts across the arms.

P 15: I it not clear whether these participants were actually “explempary adherers” as stated here. It was actually described how they chose not to tell clinicians about missed doses. It would be relevant to include a discussion about why participants are giving this information to interviewers but not clinicians. Better rapport? Or are clinicians just not asking the right questions?
We agree that they are not necessarily exemplary adherers despite having undetectable viral load. It is an important point to note that the label 'exemplary adherer' is based on clinical indicators rather than behavioural.

We have added a section into the manuscript under the subtitle: Holding back ‘truths’ in the clinic.

P 15: “perceptions of themselves, health and HIV” seems quite vague/unfocused…

We have revised this to instead read: and their confidence in discerning the psychological effects of treatment.

P 16: “data in the quantitative adherence… the clinical database” this refers to data that have not been reported here?

This has removed as we did not have space to adequately explain it.

P 17: The conclusion uses some rather general terms, e.g. “so many participants” and “early adjustments”. It would be more useful if these issues were described so that readers were left with a better impression e.g. of how much time was usually needed for adaption. It is not clear if this is a few weeks or several months…

Thank you for this suggestion. We have amended the conclusion so that it is more specific. We instead say that: As such our findings emphasise the importance of incorporating a package of interventions to accompany any roll-out of SCT to support young people in adapting to their new routine. We would anticipate that specific support should be provided for 112-16 weeks to accompany the adaptation period for those switching to SCT and that this should be preceded by a 2-4 week preparation period of education and counselling to alleviate concerns and ensure effective understanding about the weekly 2 day break. Participants suggested that such an intervention during this period may be further strengthened by incorporating peer support from those already on SCT. Any intervention should be subject to ongoing evaluation.

Reviewer: 2

Reviewer Name
Katerina Christopoulos

Institution and Country
University of California San Francisco
USA

Please state any competing interests or state ‘None declared’:
Recipient of grant funding from the National Institutes of Health
Scientific Advisory Board Member, Roche
Community Advisory Board Member, Gilead

Please leave your comments for the authors below
The submitted manuscript describes a qualitative sub-study of the BREATHER randomized clinical trial, which compared 5 days on/2 days off antiretroviral therapy to continuous antiretroviral therapy for youth aged 8-24 years. It is so refreshing to see qualitative work integrated into the conduct of this kind of trial and this well-written manuscript has the potential to make an important contribution to the literature. However, there are several issues that limit enthusiasm for the manuscript in its current form. As an overarching comment, I suggest that the authors review and address the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist, as it would be a systematic way to address many of the outstanding methodologic questions readers may have.

Critical information is missing from the methods section, particularly with regard to the research team, data collection, and the coding process. Who conducted the interviews? Were interviewers known to the participants? Were they involved in the analysis? How long were the interviews and where did they take place? Were participants reimbursed for participation?

Thank you, we have now added considerable detail to the methods section which addresses the gaps that you identify. This information has been added into the manuscript across pages 8, 9 and 10. Below is a response to your questions.

The interviews were conducted by SB in the UK and USA and by SN and another Ugandan researcher, none of whom were known to the participants prior to the study and all of whom were involved in the analysis. We have included within the results section that the participants attributed this distance to the researchers as one reason for feeling comfortable to talk to us. The interviews lasted between 45-90 minutes. All but one interview took place within the clinic, which at the request of the participant took place in their home. Participants were reimbursed for their participation to a level in line with local standard research practices.

How was the interview guide developed? Interviewing a 10-year-old is likely to be quite different from interviewing a 24-year-old. If there are standard techniques to maximize the success of qualitative work with children, the authors should describe what they are and whether these were employed.

The research team have considerable experience in conducting research with young people and children in both high and low income countries and developed the interview guides collaboratively. For each phase the guide was developed to have uniform key area of investigation but not a list of prescribed questions. As such while it had an overarching similarity in focus for all interviews, the guide was flexible enough to ensure that the interviewer could adapt the form and nature of the questions to the individual in front of them. This enabled us to respond to the individual's particular circumstances and maturity levels, for example in talking about their HIV status, rather than adopting a fixed but reductive age determined approach. We have used a similar approach in a number of studies with this age group on challenging topics with consistent success.

Who coded the data and what was the coding process? Were some codes determined a priori based on the interview guide? What was the concordance between coders? Can the authors report a kappa statistic? The authors describe the use of negative cases but no negative cases are presented in the results. Were there any participants in the SCT arm who preferred continuous therapy?

The data was analysed by the research team. A discussion was held after each interview to consider emerging analytical ideas and opportunities to refine the interview guide and approach. The coding was done inductively and individually developed. These preliminary codes were then exchanged amongst the team, discussed and reconciled into an agreed coding framework which was subsequently applied to the data.

The authors describe the use of negative cases but no negative cases are presented in the results. Were there any participants in the SCT arm who preferred continuous therapy.

Thank you for this suggestion. While there was considerable uniformity amongst participants on both arms that SCT was a great idea and eased adherence in the longer term, there was one participant who chose to move to the continuous arm from SCT because she was not able to adapt to the change in routine. This participant was exceptional because everyone else described being able to adapt and that the benefits outweighed the challenges at the beginning. However, this demonstrates the significance of the adaptation period and the potential benefits of providing tailored support to young people as discussed below. This deviant case has been added into the manuscript on page 14.

We are told repeat interviews were conducted but not the criteria for how far apart they had to be or how far into trial participation the first interview could occur. Understanding the timing of the interviews helps interpret the results and would strengthen the conclusion in the abstract that support and

education be provided for 3 months to allow adaptation. Also, did all 43 participants undergo repeat interviews? Or were interviews halted when saturation was achieved?

The following information has now been added on page 8-9. The first interview, conducted towards the start of the trial (Uganda, UK and USA) explored attitudes towards taking HIV treatment and how doing so fit in, or not, with their daily lives and priorities. The second interview, conducted at least 9 months into the trial (Uganda, UK and USA), focused on their experience of being in the trial, including SCT. The third interview, conducted towards the end of the trial and/ or as they moved into the follow-up stage of the trial (Uganda and UK) when many of them had been in the trial for more than two years, looked at their ongoing experience of the trial and their preferences for future treatment options. The focus group discussions (FGDs) were only conducted in Uganda and done after the trial findings had been explained to participants.

There was no discussion of the challenges in adapting to SCT within the first interview, although many participants would have been going through this at the time of being interviewed. They described the challenges that they encountered adapting to SCT in the subsequent data collection waves, with all but one describing having adapted to SCT within about 10 weeks. The fact that they did not mention these problems in the first interview may reflect that it is easier to identify a problem once it has been addressed, but also the increasing confidence that participants had in what they could tell us as they also told us of their concerns that if they voiced problems with SCT earlier they would be unwillingly out into the CT arm. This detail has been added on page 12.

All 43 participants were interviewed more than once. As described above the third phase was just done in Uganda and in the UK. The focus group discussions were just done in Uganda. Phase 3 was not conducted in the US due to funding. In the UK although we conducted a third phase, we only completed 3/7 interviews due to limited engagement of participants and significant staff changes in the availability of the research team.

As mentioned in response to reviewer 1's comments there was considerable consistency across the sites in terms of our findings. However, recruitment was more difficult in the UK site. This in part, as described earlier, may reflect the high saturation of research being conducted within this relatively small clinical population. But it also may speak to some of what we have learnt about why SCT is so popular. SCT is valued because it gives them the opportunity to reduce the amount of time that they had to devote to managing their HIV- through remembering to take their treatment, incur the risks of being seen taking it and feel the side effects of taking it. In line with this in the UK they wanted to come to the clinic as infrequently as they could. Participating in the trial and then in the qualitative study too entailed additional and unwanted visits.

Our sampling in the UK and USA was to include as many people as were eligible to participate within the timeframe of our fieldwork. In Uganda, when we had interview 26 participants we reached theoretical saturation. Our design was then to follow up all those who participated in phase 1 across the sites.

Half of the sample is from Uganda, yet less than half of the Ugandan participants approached agreed to participate in the qualitative study. The authors should discuss whether: 1) there were differences between developed and developing world sites, and; 2) whether the Ugandan sample may be biased toward “compliers.”

As described above we interviewed eligible Ugandan participants until we reached theoretical saturation. As discussed above we found that we encountered more challenges in recruitment and engagement in the UK than we did in the USA and Ugandan sites. We do not consider that the Ugandan sample would be biased towards compliers above and beyond the other sites. A necessary

inclusion criterion of the trial which is only those with an undetectable viral load has arguably biased the whole trial to compliers, but this is not a feature of the qualitative study beyond that we had to recruit from within the trial. We also consider that this is an additional strength of including the participants' reflections on how other young people, admittedly in their opinion, would view SCT.

It would be helpful to know the age of the participant in addition to the country and trial arm. Were any differences observed by age?

We have emphasised in the manuscript on page 8 that there was no significant difference in age, except in relation to the tone and style in which they described their experiences. We do not include the age of the participant in the detail given about each extract, as we did not consider it to be significant and not doing so helps us maintain anonymity in our reporting.

The initial concerns of participants and the adaptation period required are nicely described.

Very nice information on how stable viral load can justify non-disclosure of adherence issues. I'm not sure the first two quotes with regard to side effects add anything; the last quote may be sufficient.
Thank you we have amended this.

The idea of SCT as progress and reward is important and intriguing but the quote provided does not entirely support the claim. Are there additional quotes?
More illustrative quotes have been added.

The authors appropriately acknowledge that the acceptability of SCT applies only to the trial population.

In the Discussion, the authors mention that qualitative findings regarding adherence are different than data from quantitative surveys and adverse event reporting but the reader is not told what the quantitative findings and this comparison is not outlined in the background or methods.
As we do not have space to explain this fully this section has been removed.

One obvious question is whether any participants in the continuous therapy arm self-interrupted treatment due to participation in the trial, that is, they crossed themselves over to the intervention arm. They all talked about this being a risk now that they knew the findings of the trial to be that SCT was non-inferior and described being tempted to. But no one actually said that they were doing it. This is now described in the added section on the response to the trial findings on pages 20-21

VERSION 2 – REVIEW

REVIEWER	Katerina Christopoulos University of California San Francisco USA Recipient of NIH funding (current) Scientific Advisory Board Member, Roche (past) Community Advisory Board Member, Gilead (past)
REVIEW RETURNED	06-Dec-2016

GENERAL COMMENTS	Information on the number of coders and/or uploading the coding framework as an appendix would be helpful. Would upload COREQ checklist if required by journal.