Reviewer's report

Title: Could caregiver reporting adherence help detect virological failure in early treated Human Immunodeficiency Virus-infected infants? Experience from the PEDIACAM study in Cameroon

Version: 2 Date: 14 April 2015

Reviewer: Consuelo Beck-Sague

Reviewer's report:

This is a fine paper, which requires some revisions.
None are Major Compulsory Revisions. However, there are 15 Minor Essential Revisions.

Several are grammatical errors and/or sentences that are incomplete or have some little editing "glitch". 10 are more significant issues, and are accompanied by extensive suggestions for editing and revision and a reference (which does not have to be cited, but which informs the suggestions to the authors). Numbers 1 and 12 are the most important suggested revisions.

General:

This is an interesting study, and makes an important contribution. There are some factual (incorrect) statements, exaggerations and generalizations, and mischaracterization of what is in essence an evaluation of a strategy to assess adherence. It is a fine evaluation of the adherence-assessment strategy and it is innovative and interesting to assess it as if were a “diagnostic” test.

But it cannot really be characterized as a “substitute” for a laboratory test, and viral loads are not diagnostic tests in this setting. They are used to monitor response to cART. Moreover, few “tests” with a negative predictive value of 75% would be considered a good “stand alone” tests, let alone with the far lower positive predictive value.

Finally, there is insufficient discussion of what is one of the most compelling findings in the study: that the majority of infants and children with virological failure whose caregivers report near-perfect adherence in fact have infection with resistant strains. Not only is there insufficient discussion of this important finding, but the statement “Other factors which were not assessed by our study may be involved, such as resistance to ARV,...” suggested that this factor, which in fact was assessed, had not been assessed, and some suggestion that caregivers exaggerate adherence, when in this case, there is proof that most cases of discrepancy between adherence and virological response may be due to resistance and not to exaggeration of adherence.

Minor Essential Revisions

Abstract:
1) “Unfortunately, it is too expensive for resource-poor settings.”

This statement has to be nuanced. The cost at any given time of a relatively newly-introduced strategy is often extremely artificial and fluid. In April 2014, the price for a viral load “paid by wholesalers ranged from $11 to $25 and the final price from $18.62 to $36.38...There was a wide range of costs actually paid by African countries, however. Two, Kenya and Uganda, had knocked the price per test down to $10.50 while neighbouring Tanzania paid the region’s highest price at $55.” (http://www.aidsmap.com/Can-we-provide-point-of-care-viral-load-tests-in-poor-countries/page/ Accessed April 14, 2015).

2) “We aimed to measure the diagnostic value of caregiver reporting adherence for detecting virological failure in routine practice during the first 2 years after early initiation of cART in infants.”

This statement has to be nuanced and modified. While the adherence measure was being assessed with tools often used to assess a “diagnostic test”, which is interesting, it was not actually a diagnosis as such (presence or absence of illness) but response to treatment.

3) Since the definition is of virological failure is highly variable, it should be defined in the abstract.

4) “However, cumulative missed dose may be useful for the detection of virological success, particularly after 12 months of cART, given its high negative predictive value.”

Please, consider editing this statement; something like the cumulative missed dose measurement may be a reliable predictor of virological success, particularly...

Introduction

5) “Viral load is the best marker of adherence to cART”

Actually, viral load measurements are the best markers of RESPONSE to cART which (in patients whose strains are susceptible to the antiretroviral treatment they are receiving) is strongly reflective of adherence to cART. It is thus an excellent marker for the main objective of cART (viral suppression). Adherence is a means to this end, not an end in itself. This statement needs to be nuanced.

6) “…but is too expensive for routine use in resource-limited settings.”

See above Abstract. Viral loads are being used routinely to monitor response to cART in many resource-limited settings at very reasonable costs.

7) “…there is a corresponding need for reliable methods, cheaper than viral load determinations, for assessing infant adherence to cART in routine practice.”

Again, this statement needs nuancing. Evaluation of how much correlation there
is between reported adherence and response to ART is definitely indicated, as is assessment of infant adherence per se. However, the idea that the reason for this is to substitute viral load determinations with something cheaper does not follow.

8) “The main objective of this study was to assess the diagnostic values of caregiver adherence reporting questionnaires for detecting virological failure in routine practice during the first 2 years of cART in infants in Cameroon.”

The grammar here (diagnostic values) is awkward. The term “diagnostic values” (plural) is being used as a synonym for sensitivity-specificity evaluation. Suggest using an alternative, such as “…was to assess the sensitivity, specificity and positive and negative values of caretiver reports of poor adherence for detecting virological failure in…”

Methods

9) “The inclusions in PEDIACAM were organized in two phases and are described elsewhere (18)…”

Recommend “the inclusion criteria”.

Discussion

10) “Here, prevalence of virological failure was low: 47.8% at M3, 23.8% at M12 and 27.9% at M24, which explains the high NPV. A cohort study in Uganda reported that 28.8% (17/59) of children had viral loads #1000 copies/mL at M12, and this is consistent with our findings (20).”

Obviously, this is a relative thing. In some pediatric populations, a virologic failure of 47.8% defined as >1000 copies per mL would be considered low, and in others, quite high. Recommend qualifying this statement.

11) “Other children were classified as “adherent” although they showed virological failure at M12 or M24, leading to false negative cases and subsequently to decreased sensitivity, NPV and LR-.”

Consider instead of "leading to false negative cases" "which would be considered false negatives, reducing the sensitivity, NPV and LR- of ‘adherence’ as a test for virological failure"

*12) “Other factors which were not assessed by our study may be involved, such as resistance to ARV,…”

This is a baffling statement. One of the most important and powerful findings in this study is that of the 11 “divergent” unexpected results (virologic failure in patients whose caregivers reported near-perfect adherence), 7 had genotypic evidence of resistance to antiretrovirals in their regimens. This is easily one of the most powerful findings not only relevant to the frequency of resistance in this population, but also, to the fact that the other factors (caregiver desire to please providers, etc.) account for a minority of discrepant adherence-virological response findings. Obviously, this factor WAS assessed by the study, and the surprising findings should give us clinicians pause when we exaggerate the
unreliability of caregiver histories, as well as when we (conversely) suggest that caregiver histories can be used to substitute for viral load testing.

The findings from this study strongly suggest that in the majority of cases, patients whose caregivers report high adherence and have virological failure have resistance mutations.

13) Table 1
CD4 count (%) at cART initiation (median, IQR) 161 23 (15 ; 32)
Please, clarify; 23 is presumably the median % of lymphocytes that are CD4+, right? And the IQR is 15-32%, right?

14) Table 2:
[400-1000] should be 400-1000, right? No brackets needed. If brackets used, suggest \([400-1000]\).

Grandmother is not normally hyphenated.

15) Table 3 Title: Suggest --Value of reported adherence for detecting virological failure in HIV-infected infants treated early by cART for at least 3 months

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
'I declare that I have no competing interests