



## OPEN LETTER

# Models of service delivery for optimizing a patient's first six months on antiretroviral therapy for HIV: an applied research agenda [version 1; peer review: 2 approved, 2 approved with reservations]

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## Abstract

Differentiated models of service delivery (DSD models) for HIV treatment in sub-Saharan Africa were conceived as a way to manage rapidly expanding populations of experienced patients who are clinically "stable" on antiretroviral therapy (ART). Entry requirements for most models include at least six months on treatment and a suppressed viral load. These models thus systematically exclude newly-initiated patients, who instead experience the conventional model of care, which requires frequent, multiple clinic visits that impose costs on both providers and patients. In this open letter, we argue that the conventional model of care for the first six months on ART is no longer adequate. The highest rates of treatment discontinuation are in the first six-month period after treatment initiation. Newly initiating patients are generally healthier than in the past, with higher CD4 counts, and antiretroviral medications are better tolerated, with fewer side effects and substitutions, making extra clinic visits unnecessary. Improvements in the treatment initiation process, such as same-day initiation, have not been followed by innovations in the early treatment period. Finally, the advent of COVID-19 has made it riskier to require multiple clinic visits. Research to develop differentiated models of care for the first six-month period is needed. Priorities include estimating the minimum number and type of provider interactions and ART education needed, optimizing the timing of a patient's first viral load test, determining when lay

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providers can replace clinicians, ensuring that patients have sufficient but not burdensome access to support, and identifying ways to establish a habit of lifelong adherence.

### Keywords

HIV, antiretroviral therapy, differentiated models, retention, Africa

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## Introduction

As countries around the world strive to reach global targets for HIV, including starting and retaining 95% of those diagnosed with HIV on antiretroviral treatment (ART), one of the most promising recent strategies has been the advent of “differentiated service delivery” (DSD) models for providing treatment. DSD models are approaches to delivering ART that adjust the location, timing, provider, or service delivered with the goals of making care more patient-centered, supporting treatment outcomes, and making HIV programs more efficient<sup>1</sup>. In sub-Saharan Africa, common DSD models include medication pickup points outside of health facilities, “fast-track” stations at clinics for patients to obtain medication refills without waiting in the regular clinic queue, and group models such as adherence clubs that allow patients to receive refills, adherence counseling, and other services together<sup>2</sup>. Limited existing data suggest that most of these models either sustain or improve treatment outcomes<sup>3</sup> and succeed in making treatment more convenient and/or less expensive for patients, by bringing services closer to their homes and reducing waiting times<sup>4</sup>.

Because DSD models were originally conceived as a way to manage rapidly expanding populations of experienced patients who are clinically “stable” on ART, most do not cater to newly-initiated patients. Entry requirements for most models include both a minimum number of months on treatment—usually six or 12—and a report of a suppressed viral load or comparable evidence of treatment success. In a recent review of published descriptions of DSD models in Africa, more than 70% required at least six months on ART for DSD entry, while 84% explicitly limited participation to “stable” patients<sup>5</sup>.

As a result of the requirement for clinical stability, newly-initiated patients are systematically excluded from DSD models during their first six (or 12) months on ART, no matter their conditions, needs, or viral load. They instead experience the traditional or conventional model of care for newly initiated patients, which has changed relatively little in the past decades. Although there has been some streamlining, most national guidelines continue to call for monthly visits to a clinical facility for the first six months of treatment, with only short (one to two month) drug refills.

In this open letter, we argue that this conventional model of care for a patient’s first six months on ART may no longer be appropriate, for several reasons. First, the highest rates of treatment discontinuation are in the first six-month period after treatment initiation. This has been the case since the earliest published estimates of retention rates<sup>6,7</sup> and remains the case now<sup>8</sup>. Among patients who initiated ART in the last quarter of 2018 in South Africa, for example, 30% were reported as lost to follow up by six months<sup>9</sup>. In Zimbabwe, retention in care improved significantly between 2010 and 2015 except for patients in their first six months<sup>10</sup>. Beyond the impact

on individual morbidity and mortality, early losses from care are associated with internalized stigma, leading to social isolation, fear of disclosure, and discrimination, which potentially compound the inherent challenges in returning to care<sup>11–13</sup>.

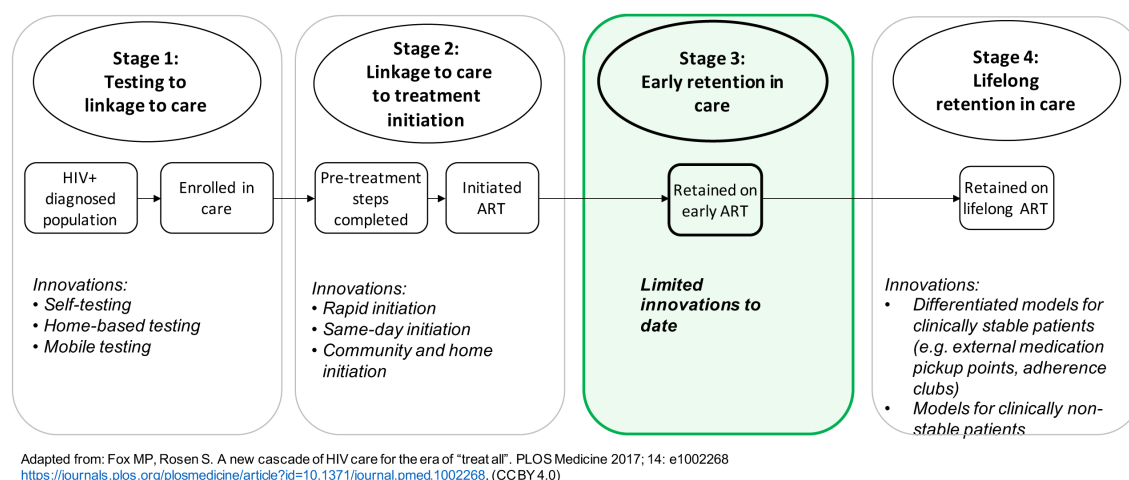
Second, while the model of care for newly-initiated patients has not changed over time, the patients and the drug regimens they are taking have. CD4 counts at treatment initiation have risen steadily since the advent of universal treatment eligibility<sup>14</sup> even as the proportion of patients with advanced disease has remained constant<sup>15</sup> and “re-initiation” of those who have previously interrupted care has become more common<sup>16</sup>. Most newly initiating patients do not need additional clinical care after ART initiation. In a recent study in South Africa, for example, 86% of patients were considered clinically well enough for same-day ART initiation, without the need for additional care<sup>17</sup>. Current antiretroviral regimens are also better tolerated than previous first-line regimens, requiring fewer drug changes<sup>18</sup>.

Third, to date, efforts at “patient-centeredness” have largely bypassed the first six months on ART. As illustrated in [Figure 1](#), innovations to make treatment more accessible in terms of time and transport costs and more satisfactory for patients do not extend to new initiators.

Fourth, while treatment guidelines have changed little for this period, procedures for initiating ART have evolved with the advent of rapid and same-day initiation<sup>19</sup>. New initiators no longer undergo multiple counseling and education sessions before initiation. As a result, it is possible—though studies conflict on this issue<sup>8,20</sup>—that patients may be less prepared in advance for the reality of daily medication adherence and regular prescription refills and thus be more likely to disengage from care early on.

Fifth, the global epidemic of COVID-19 is highlighting the potential risks of exposure to SARS-CoV-2 at healthcare facilities both for patients and staff and, due to physical distancing ordinances and lockdowns, access to ART is more difficult and expensive for patients to achieve<sup>21,22</sup>.

In response to all these factors—burdensome, dated procedures for the first six months of therapy, rapid ART initiation, patients’ improving health condition at presentation, high attrition during this period, and COVID-19—reconsideration of how to deliver ART during the first six months is warranted and overdue. In early March 2020 we convened a half-day roundtable to explore what one or more optimized models of service delivery might look like for this period. Participants included clinicians, epidemiologists, economists, HIV program implementers, funders, and advocates. After reviewing the data cited above, the roundtable focused on the specific requirements of the first six months on ART, with the discussion divided into patients’ clinical and non-clinical needs. A preliminary research agenda was then proposed for developing new differentiated service delivery models for the first six months on ART. A version of that agenda further developed by the authors is reported here.



**Figure 1. Innovations in service delivery along the HIV treatment cascade.** Adapted from 23 under a CC BY 4.0 license.

## Stratifying patient populations

A first consideration for improving care during the first six months was that patients in this population are not homogeneous. In addition to varying in age, sex, and other demographic and socioeconomic characteristics, patients differ at treatment initiation in terms of their clinical characteristics and their prior exposure to ART. While multiple criteria for segmenting populations were proposed, three major categories of patients were ultimately identified, based on patients' status at initiation: 1) clinically well, ART-naïve initiators (new initiators); 2) clinically well, ART-experienced initiators (re-initiators); and 3) people presenting for initiation or re-initiation with advanced disease. We note that "clinically well" is open to interpretation and likely includes patients who are mildly symptomatic but ambulatory and not critically ill, while the advanced disease category, following WHO guidance<sup>19</sup>, may include patients who appear well but have low CD4 counts. We also are aware that a patient's status as naïve or re-initiating is often based on self-report, as most countries do not have data systems that allow real-time monitoring of prior treatment.

Each of these three categories of patients is likely to have distinct clinical and non-clinical needs during the first six months. New initiators do not have experience with ART and should be supported with treatment education. Re-initiators, by definition, have already encountered at least one barrier to remaining in care; that barrier may well re-emerge if it is not addressed directly. Re-initiators can further be stratified by the timing of their prior disengagement in care and adherence patterns<sup>24</sup>. People with advanced disease, in addition to potentially being in poor health requiring immediate medical care, are typically presenting late, suggesting that they too may face obstacles that led them not to seek care sooner<sup>25</sup>. In this paper we focus primarily on the first category, new initiators, for whom the standard of care has changed little in recent years.

## Clinical and non-clinical requirements

Priority research questions are presented in Table 1. The first set of questions pertains to the clinical needs of patients during

their first six months on treatment. During this period, most countries require at least two, and up to six, post-initiation clinic visits when a patient is required to be seen by a clinician, in addition to receiving drug refills and adherence counseling. Most new and re-initiators do not require any clinical interventions during this period, however, provided that any conditions present at ART initiation—opportunistic infections, side effects, or other acute concerns—were addressed by the clinician responsible for ART initiation, as part of the initiation process. Re-initiators who previously stopped ART due to side effects may also be prescribed more appropriate regimens.

The other major set of questions, also shown in Table 1, pertained to the emotional, social, and other non-clinical needs of patients in their first six months. While participants were generally comfortable with the notion that frequent (monthly) clinic visits and clinical consultations are not essential for most patients after initiation, there was a consensus that some interaction with a care provider during at least the first month on ART, even if merely a text message exchange with a community health worker, remains important to securely engage patients in care for the short and long term. Beyond that, ensuring that patients have adequate information about HIV and ART and access to on-demand emotional and social support, virtually or in person, was thought sufficient.

## Other considerations

In addition to the research questions specified in Table 1, several issues were raised that were considered important for efforts to develop new models of care for the first six months. First, the quality of the ART initiation process is crucial to determining early outcomes on treatment. While same-day and rapid initiation are effective in reducing pre-initiation loss to follow up, poor quality in the initiation process will have the opposite effect on retention after initiation. At the point of treatment initiation, providers must address both acute and chronic co-morbidities, help patients identify potential adherence barriers in advance, and convey sufficient information about ART and available support services that patients can effectively

**Table 1. Priority research questions for developing models of care for the first six months on ART.**

Question	Rationale and potential data sources or study designs
<b>Questions pertaining to clinical requirements</b>	
1. Is a routine clinic visit required between ART initiation and month 6, and if so, exactly what procedures, tests, or other activities should it entail and when should it take place?	The necessity of a routine clinical visit in the first six months on ART for most patients is unclear. Existing data that might answer this question are medical records for patient cohorts in this period that contain details of visits, clinicians seen (e.g. doctor, nurse, clinical officer), and changes made as a result of the visit. If most routine visits result in no changes to the patient's regimen or other procedures or behaviors, then the visit should be dropped if it is not justified in some other way—for example, the patient who has a co-morbidity that requires more frequent consultation management or is in a risk group that requires special attention.
2. What is the optimal timing for a patient's first on-treatment viral load test? (Note that this does not refer to a baseline or initiation viral load.)	Since viral suppression is often one of the key requirements for being considered clinically "stable" on ART—and is also itself the primary goal of ART—achieving and confirming suppression as soon after initiation as possible is considered desirable. Conducting a test at 6 months, which is the norm in most countries, is likely considerably later than is optimal, given the shorter time required for suppression with current recommended first-line drug regimens <sup>26,27</sup> . Roundtable participants were mixed as to whether three or four months after initiation would be optimal, but there was no support for waiting for six months and thereby potentially delaying both eligibility for a less-intensive model of care and the patient's own peace of mind.
3. What are the main reasons for unscheduled visits in this period, and how can patients best be prepared to recognize conditions that require clinical care?	Existing data to answer this question include both observational and trial data on time to viral suppression for different patient populations and drug regimens. Such data are currently being reviewed by a WHO guideline committee to update guidance on timing of the first viral load. Both CD4 count at initiation and ARV regimen matter to this issue. We note, for example, that in the ADVANCE trial of a first line regimen containing dolutegravir, 97% of patients were suppressed (viral load less than 1000 copies/milliliter) four weeks after initiation <sup>27</sup> .
4. Can a lay provider and/or virtual contacts adequately assess clinical condition during the early treatment period and replace in-person visits with a trained clinician?	The main risk to eliminating or reducing routine clinic visits is that patients who need care will not obtain it, either because they do not recognize the symptoms, believe that they should or must wait for a routine appointment, or are unable to access the clinic for logistical or other reasons. The first two of these constraints can be addressed through better patient preparation and education at the time of ART initiation. The third is not unique to care on demand—if a patient cannot afford to access the clinic on demand, it is likely that routine appointments will also be missed. Other support mechanisms are needed in this case.  Existing data that could be used to ensure that patients seek care when needed are data sets that report reasons for unscheduled clinic visits. While routine EMR data sets in many countries often report patient condition incompletely, data from trials, adherence studies, and carefully observed cohorts should suffice.  Rather than requiring a routine clinic visit after, for example, one month on ART, a trained community health worker or another lay provider may be able to use a checklist of symptoms to screen newly initiated patients by telephone or during a home visit, avoiding the need for an in-person visit for most of these patients. It is even possible that this could be done electronically in some settings, using an on-line software application (chatbot) to send and receive text or WhatsApp messages via patients' phones. Similarly, if contact with a trained clinician is considered essential, video platforms (telemedicine) might make it possible for in-person visits to be replaced with digital consultations in some settings. Research is needed to determine if existing cadres of lay health workers can implement a process like this safely and can correctly distinguish between patients who should be referred for additional care and those who should not and if and where available bandwidth, device access, and software could support more use of electronic, rather than in-person, care <sup>28</sup> .
<b>Questions pertaining to non-clinical requirements</b>	
5. How much non-clinical interaction with healthcare providers is optimal between ART initiation and eligibility for an existing, stable-patient model of care?	Individual patients vary widely in their needs and expectations for contact with lay or professional healthcare providers. As mentioned above, roundtable participants thought that at least one interaction during the first month after initiation is essential, both to confirm that the patient is responding well to treatment and to establish a pathway for communication with which the patient is comfortable. Beyond this interaction in month 1, research is needed to know which patients would benefit from additional contact; when, where, how, and with whom such contact should be; and the best pathways to ensure that patients who would benefit do receive such support.



Question	Rationale and potential data sources or study designs
6. What is the best way to ensure adequate HIV and ART knowledge (education) among newly initiated patients?	Roundtable participants noted that "treatment education" has diminished in recent years, as the process of ART initiation has accelerated, and believed that a lack of understanding of HIV and ART is partly responsible for the high rates of early attrition observed. Data are sparse, though, on what encompasses sufficient understanding or how best to ensure it, without burdening patients with additional clinic visits or delaying treatment initiation. Research on different approaches to delivering treatment education in a manner in which it is likely to be retained is also needed.
7. Are there specific additional services or approaches that would help patients establish a long-term habit of ART adherence?	The early treatment period is critical not only to rebuild immune function and achieve viral suppression but also to instill in new patients a lifelong habit of adherence to treatment. Roundtable participants recognized that there is a behavioral science literature on habit formation that may offer insights into how to strengthen antiretroviral adherence, and that this literature should be accessed to develop potential early interventions to improve long-term outcomes. Research patient preferences for services, for example using discrete choice experiments, is also needed.
8. What is the role of disclosure in promoting early retention, and should there be explicit support for disclosure during this period?	Existing research indicates that fear of disclosure and discrimination are among the causes of early losses from treatment <sup>11-13</sup> . It is unclear, though, whether support to patients for disclosure and/or other interventions to reduce barriers such as stigma and interpersonal violence are essential during the first six months on treatment and, if so, for whom, by whom, and how they should be delivered. For patients who do need such support, intervention during the early treatment period may be a prerequisite to achieving retention on ART. Various peer-based interventions have been tried <sup>29,30</sup> , but research is still needed on an optimal approach to delivering disclosure support and, importantly, to determine which patients would benefit from such support, without burdening those who would not.
9. Should patients opt in, opt out, or "qualify out" of components of specific non-clinical aspects of support, and how should this be managed?	Ideally, treatment programs will be able to offer patients a choice of ART retention-related services tailored to the early treatment period, such as adherence counseling, home visits, and virtual interactions. It is unclear if such services should follow an "opt-in", "opt-out" or "qualify out" model to achieve retention targets and increase patient satisfaction. By "qualify out", we mean that both the provider and the patient should be confident that the patient has sufficient treatment knowledge, understands what HIV- and ART-related conditions should trigger a phone call or clinic visit, and has access to a working phone. This question is related to the broader issue of how responsibility for retention on ART should be allocated between providers and patients and the extent to which patients should be offered choices in service delivery.
10. What additional or different non-clinical services are needed for re-initiators?	By definition, ART re-initiators have already experienced one or more barriers to retention in care that were sufficiently serious to cause disengagement. Simply re-initiating ART without identifying and addressing those barriers seems unlikely to achieve long-term retention for most of these patients. Research is needed on how providers can most effectively support this process without creating even more barriers, for example by requiring additional clinic visits for adherence counseling.

manage their own care going forward. More attention should thus be paid to the quality of the initiation process, as well as its speed.

Second, any new models of care proposed for the early treatment period must be able to withstand incomplete or poor fidelity to guidelines and unreliable access to resources. Complicated models that will be effective only if providers closely follow guidelines and/or have access to items that may suffer stock-outs are not likely to succeed. The same conditions should apply to research methods used in evaluations of new models of care; study designs must be robust to non-compliance with guidelines and secular changes that affect both intervention and comparison groups.

Third, the possibility was raised of triaging patients to more or less intensive retention support at the time of ART initiation, based on patient characteristics. If higher and lower risk patients could be identified at the start, providers could potentially offer tailored support plans to those at higher risk, while allowing those at lower risk to proceed with less intervention. Unfortunately, at this point, data on practical predictors of poor retention do not exist, despite efforts to create risk indices<sup>31</sup>. Further research in this area may also be of value.

Finally, patients who present with advanced disease require different approaches than the majority who have no or mild symptoms. Clearly those who are acutely ill need immediate care, regardless of the burden it imposes. Current guidelines and practices, however, generally require even asymptomatic patients with low CD4 counts to make additional clinic visits. If these patients have advanced disease because they face challenges in seeking treatment, and thus presented late, simplifying care during the first six months may be even more important for them than for healthier patients.

## Conclusion: the role of COVID-19

The advent of the COVID-19 pandemic is rapidly changing national guidelines and practice in HIV treatment. Many

countries have begun to extend the duration of ART refills at treatment initiation and reduce clinical encounters during the early treatment period. These changes are occurring rapidly, and implementation is likely uneven across regions and individual facilities and programs. Evaluation of the outcomes of these measures is essential, as they provide a natural experiment with different approaches to initiation and early treatment. As the COVID-19 crisis recedes, data on steps that were taken and their effects on patient welfare will be a critical source of information for improving the early treatment algorithm in the future. These data will add to our evidence base on what services can effectively be provided outside of clinic facilities or remotely, and under what circumstances.

## Data availability

No data are associated with this article.

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# Open Peer Review

Current Peer Review Status:    

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Reviewer Report 28 August 2020

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**Christopher J. Hoffmann**

Johns Hopkins University, Baltimore, MD, USA

Thank you for the opportunity to review the Open Letter “Models of service delivery for optimizing a patient’s first six months on antiretroviral therapy for HIV: an applied research agenda.” This commentary was written by leading researchers in the field following a Round Table that included prominent academicians and thinkers. The authors provided well written and well laid-out arguments for identifying and evaluating new approaches to improve care outcomes during the first 6 months after ART initiation. The justification for identifying effective approaches to improve early ART care are clear: loss from care is high during the first 6 months after ART initiation. Little work has specifically focused on adjusting the care model to overcome some of this loss from care. The authors make an effective argument that this period needs to be part of the care model conversation and included in focused research. Finally, the authors provide a list of research questions that, if answered, could help to inform new care models for this period of care. Overall this is a nice contribution to the discussion on improving early care outcomes.

I have the following comments and suggestions:

1. Although the Round Table included leading researchers, mostly from the global north, the list of participants appeared to lack balance. The perspective of implementers on actual adaptation from some of the standard traditional practice may have added depth.
2. Some discussion and examples of adaptation from standard practice would be helpful for the reader to see what innovation is occurring. Innovation is suggested by the finding that 70% of differentiated care programs are for people who have completed at least 6 months of ART. This implies that 30% of differentiated care programs include components for people with <6m of ART. Describing some of these approaches would be interesting. Further adaptation has also occurred with COVID-19, with efforts to reduce clinic visits, even after ART initiation. Although these may not be part of an evaluation, some description of adaptation of early ART management to reduce clinic contact due to COVID-19 would be useful as well. This could also reinforce the need to understand what actually works best as change is occurring.

3. The authors list internalized stigma (I assume HIV stigma and not shame from early loss from care) as an important reason for early loss from care. It would help to understand what new model of care could effectively address this issue. There are other reasons for early loss from care related to the cost (opportunity and financial) of repeat clinic visits, etc. that are easier to see how a change to care models could shift the balance from cost to value for a patient. It suggests adding a list of some of the reported causes of early loss from care which have been reported in multiple qualitative studies.
4. Figure 1 nicely illustrates the focus of this commentary and the gap in tested innovations in this space.
5. The priority research questions are all reasonable and presenting discrete questions is useful. However, I believe that as presented it isn't clear that there is a single (patient centered) goal to achieve at 6 months and subsequently. Ideally the metric for assessing these components fits into that goal and the other components of care for the first 6 months.
6. It was interesting that psychosocial support was not clearly mentioned in the Table in light of internalized stigma being presented as the only example of reasons for early care disengagement. What, how, and to whom seems important in this regard (and has been the subject of study with peer supporters, digital support, and more traditional HIV support groups).

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Partly

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Yes

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** HIV implementation science with a focus on optimizing care outcomes and survival for people with HIV in low and middle income countries.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have**

**significant reservations, as outlined above.**

Author Response 05 Oct 2020

**Sydney Rosen**

Comment: Overall this is a nice contribution to the discussion on improving early care outcomes.

**Response:** Thank you.

Comment: 1. Although the Round Table included leading researchers, mostly from the global north, the list of participants appeared to lack balance. The perspective of implementers on actual adaptation from some of the standard traditional practice may have added depth.

**Response:** We agree entirely about the limitations of the roundtable participants. The reason is that the roundtable was an opportunistic event scheduled to coincide with the Conference on Retroviruses and Opportunistic Infections (CROI), which is held in the United States and is primarily a research meeting. Participants were thus CROI attendees, who come mainly from North America and Europe and are mainly scientists, not implementers. We agree that more active participation from implementers is needed as the preliminary research questions we proposed are developed into studies and evaluations.

Comment: 2. Some discussion and examples of adaptation from standard practice would be helpful for the reader to see what innovation is occurring. Innovation is suggested by the finding that 70% of differentiated care programs are for people who have completed at least 6 months of ART. This implies that 30% of differentiated care programs include components for people with <6m of ART. Describing some of these approaches would be interesting. Further adaptation has also occurred with COVID-19, with efforts to reduce clinic visits, even after ART initiation. Although these may not be part of an evaluation, some description of adaptation of early ART management to reduce clinic contact due to COVID-19 would be useful as well. This could also reinforce the need to understand what actually works best as change is occurring.

**Response:** We thank the reviewer for this suggestion. Although it does seem as though 30% of programs do not require < 6 months on ART, we were not able to find any evaluation results for models of care for those on ART < 6 months either in the literature or identified by roundtable participants. We are aware of one model that enrolls newly initiated patients, a mobile ART program in Zambia, but the evaluation of this program has not yet been published. We are reluctant to call attention to models whose effectiveness is not yet known. Adaptations resulting from COVID-19 are very new and had not occurred at all when our article was written. As we recommend at the end of the article, these adaptations should be evaluated as soon as possible, to provide the information that the reviewer mentions is needed.

Comment: 3. The authors list internalized stigma (I assume HIV stigma and not shame from early loss from care) as an important reason for early loss from care. It would help to

understand what new model of care could effectively address this issue. There are other reasons for early loss from care related to the cost (opportunity and financial) of repeat clinic visits, etc. that are easier to see how a change to care models could shift the balance from cost to value for a patient. It suggests adding a list of some of the reported causes of early loss from care which have been reported in multiple qualitative studies.

**Response:** In the article we note that internalized stigma may result from early loss from care, rather than being itself a reason for loss from care. We regard it as one of the harms that may result from having an inappropriate model of care that promotes patient attrition, and thus one of the justifications for needing new models of care during the early treatment period. We did not provide a list of reported causes of early loss from care because these have been reported in multiple prior publications, as the reviewer notes.

Comment: 4. Figure 1 nicely illustrates the focus of this commentary and the gap in tested innovations in this space.

**Response:** Thank you.

Comment: 5. The priority research questions are all reasonable and presenting discrete questions is useful. However, I believe that as presented it isn't clear that there is a single (patient centered) goal to achieve at 6 months and subsequently. Ideally the metric for assessing these components fits into that goal and the other components of care for the first 6 months.

**Response:** With apologies, we do not understand this comment. Presumably the goal of most treatment programs is for the maximum number of patients possible to be retained in care and virally suppressed and have a high health-related quality of life by six months after treatment initiation, but some programs for some populations may have additional or other goals. In the first section of this article, we mention several potential aims of improved models of care, including better retention, better "patient-centeredness," and reduced exposure to COVID transmission.

Comment: 6. It was interesting that psychosocial support was not clearly mentioned in the Table in light of internalized stigma being presented as the only example of reasons for early care disengagement. What, how, and to whom seems important in this regard (and has been the subject of study with peer supporters, digital support, and more traditional HIV support groups).

**Response:** As explained above, we do not regard internalized stigma as a cause of early loss to care, but rather as an effect. Question 5 addresses how much support patients need; research on the importance of social support of different types (by whom, how, frequency) would fall under this question.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 25 August 2020

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**Peter Bock** 

Desmond Tutu Tuberculosis Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Many thanks for the opportunity to review this really important and well-written letter, some comments on the content below.

**Major comment:**

- Overall I think these research questions listed are very limited in scope and seem highly context specific - would there not be scope for a programmatic cluster trial that evaluated a package of care?

**Minor comments:**

- As countries around the world strive to reach global targets for HIV, including starting and retaining 95% of those diagnosed with HIV on antiretroviral treatment (ART)* - Does this refer to UNAIDS targets – not sure if exactly correct? Please reference.
- Each of these three categories of patients is likely to have distinct clinical and non-clinical needs during the first six months.* - This is a good point but there is also an argument for problems with having too differentiated an approach at the busy interface between healthcare staff and clients. Also there is a risk of making these assumptions – albeit it is a good idea without unequivocal evidence so there is a balancing act that may be worth referring to? But I see you make these points well later on.
- I think the point you make about emphasising support for HIV positive patients with advanced disease is a good one and doesn't require further evidence.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Partly

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Partly

**Is the Open Letter written in accessible language?**



Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** HIV treatment and prevention

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 05 Oct 2020

**Sydney Rosen**

Comment: Overall I think these research questions listed are very limited in scope and seem highly context specific - would there not be scope for a programmatic cluster trial that evaluated a package of care?

**Response:** We agree that most research questions pertaining to service delivery are context-specific, for this and most other topics, and we thank the reviewer for pointing this out. The research questions we proposed were intended to be context-specific to the extent that they reflect our understanding of conditions in many sub-Saharan African countries. Even within countries, though, we agree with the reviewer's implication that the effectiveness of interventions is very locally determined. Models that work well with one patient population may not be effective in another. Similarly, models that are feasible in one location—such as a densely populated urban settlement—are not likely to be feasible in another, such as a rural community. For that reason, all the research questions we proposed should be tailored for the setting in question.

Comment: As countries around the world strive to reach global targets for HIV, including starting and retaining 95% of those diagnosed with HIV on antiretroviral treatment (ART) - Does this refer to UNAIDS targets – not sure if exactly correct? Please reference.

**Response:** We agree this comment should be referenced. The citation is: UNAIDS. Understanding fast track: Accelerating action to end the AIDS epidemic by 2030. Geneva: UNAIDS, 2015. Available at: [https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2020/july/20200706\\_global-aids-report](https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2020/july/20200706_global-aids-report).

Comment: Each of these three categories of patients is likely to have distinct clinical and non-clinical needs during the first six months. - This is a good point but there is also an argument for problems with having too differentiated an approach at the busy interface between healthcare staff and clients. Also there is a risk of making these assumptions – albeit it is a good idea without unequivocal evidence so there is a balancing act that may be worth referring to? But I see you make these points well later on.

**Response:** We agree that asking busy healthcare staff to make detailed assessments at a client's first visit is impractical. The three categories we identified, however, are sufficiently different that it seems reasonable to expect healthcare staff to be able to distinguish among them without too much difficulty. We are glad that we were able to address this sufficiently later in the paper.

Comment: I think the point you make about emphasizing support for HIV positive patients with advanced disease is a good one and doesn't require further evidence.

**Response:** Thank you.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 24 August 2020

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**Richard Lessells** 

KwaZulu-Natal Research Innovation & Sequencing Platform, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

This open letter lays out the rationale for developing differentiated models of care for people starting antiretroviral therapy and in the first six months (not just people who are established on ART and stable), and includes a proposed research agenda to guide the development. This stems from a technical roundtable discussion held in early 2020 involving a number of clinicians, epidemiologists, implementers, health economists, advocates and funders involved in HIV treatment and care in sub-Saharan Africa.

The authors make a strong argument why the development of innovations in this period are important, and it's an argument that I certainly agree with. The priority research questions are sensible and pretty comprehensive. This is a good starting point to stimulate more ideas in this area and to help guide this research agenda.

I have a few minor comments that could be considered by the authors:

1. Introduction, p3: On the fifth point that the COVID-19 epidemic has highlighted the potential risks of exposure to SARS-CoV-2 at healthcare facilities, I thought it might be worth pointing out here that of course we have also been aware for a long time of the risk of exposure to TB in healthcare facilities (for patients and healthcare workers) and have not done enough to mitigate this risk.

2. Table 1, Clinical requirements: I think an important point that is mentioned in the text but not really covered by any of the research questions is the integration between care delivery for HIV and other chronic diseases. Innovative models of HIV care in this time period will have limited impact for an individual if they still have to attend a clinic every month for their hypertension or diabetes medication. So understanding what people's clinical needs are outside HIV care would be important. Was this discussed in the roundtable? Could there be a question framed around this issue?
3. On a similar point around need for integrated care, for question 3 I think it might be worth highlighting the need to identify the main HIV-related and non-HIV-related reasons for healthcare visits.
4. Other considerations, p7: On the point about triaging patients to different levels of retention support at the time of ART initiation, the valid point is made that we have never identified consistent reliable predictors of poor retention. The statement is made that 'Further research in this area may also be of value'. One could argue that if we haven't found reliable predictors by now, we probably aren't going to no matter how much research we do. So I think this statement could be strengthened by explaining why further research might be worthwhile – what would be different from all that has been done already?

I have one additional comment that does not relate directly to the manuscript but to the broader process. I note that, although all the authors and roundtable participants are all involved in HIV research in Africa, the majority (of authors and roundtable participants) are not from Africa but from North America and Europe. I hope that there is a commitment on the part of the authors, funders and other drivers of this research agenda for more active participation from African scientists, clinicians, implementers, and policy makers as this moves forward.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Yes

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** HIV treatment and care, HIV epidemiology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 05 Oct 2020

**Sydney Rosen**

Comment: The authors make a strong argument why the development of innovations in this period are important, and it's an argument that I certainly agree with. The priority research questions are sensible and pretty comprehensive. This is a good starting point to stimulate more ideas in this area and to help guide this research agenda.

**Response:** We thank the reviewer and are glad that the questions seem sensible and comprehensive.

Comment: 1. Introduction, p3: On the fifth point that the COVID-19 epidemic has highlighted the potential risks of exposure to SARS-CoV-2 at healthcare facilities, I thought it might be worth pointing out here that of course we have also been aware for a long time of the risk of exposure to TB in healthcare facilities (for patients and healthcare workers) and have not done enough to mitigate this risk.

**Response:** This is a good point; minimizing patients' exposure to healthcare facilities, particularly in the first six months on ART, when CD4 counts may remain low, will also reduce TB risk.

Comment: 2. Table 1, Clinical requirements: I think an important point that is mentioned in the text but not really covered by any of the research questions is the integration between care delivery for HIV and other chronic diseases. Innovative models of HIV care in this time period will have limited impact for an individual if they still have to attend a clinic every month for their hypertension or diabetes medication. So understanding what people's clinical needs are outside HIV care would be important. Was this discussed in the roundtable? Could there be a question framed around this issue?

**Response:** We thank the reviewer for raising this issue. It is true that improving models of HIV care is less valuable if service delivery for co-morbid conditions is not improved at the same time. We did not discuss this issue at length at the roundtable, but we should have. We do mention it in the first paragraph under "Other considerations," noting "At the point of treatment initiation, providers must address both acute and chronic co-morbidities." We agree, however, that a research question addressing it should be added to the proposed research agenda.

Comment: 3. On a similar point around need for integrated care, for question 3 I think it might be worth highlighting the need to identify the main HIV-related and non-HIV-related reasons for healthcare visits.

**Response:** Yes, it would be useful to know the proportion of patients who make non-HIV related facility visits during their first 6 months on ART, as input data for optimizing and integrating care during this period. The challenge for generating this information is that in

many (most?) settings, patient records for HIV care are separate from records for all other primary healthcare and often not linked with a common identifier other than patient name and date of birth. It is thus difficult to create a data set that includes non-HIV visits for HIV patients. It is likely that some clinics or programs do use a common patient record, and locating such a data set in order to identify and quantify non-HIV reasons for healthcare visits would be of value.

Comment: 4. Other considerations, p7: On the point about triaging patients to different levels of retention support at the time of ART initiation, the valid point is made that we have never identified consistent reliable predictors of poor retention. The statement is made that 'Further research in this area may also be of value'. One could argue that if we haven't found reliable predictors by now, we probably aren't going to no matter how much research we do. So I think this statement could be strengthened by explaining why further research might be worthwhile – what would be different from all that has been done already?

**Response:** Hope springs eternal. The value of being able to predict poor retention is so high that it seems worth continuing to look for predictors that are reliable and feasible to collect. We acknowledge that this may be futile, but it's possible that there are characteristics of patients or facilities, or combinations of these, that could help triage patients for more or less retention support.

Comment: I have one additional comment that does not relate directly to the manuscript but to the broader process. I note that, although all the authors and roundtable participants are all involved in HIV research in Africa, the majority (of authors and roundtable participants) are not from Africa but from North America and Europe. I hope that there is a commitment on the part of the authors, funders and other drivers of this research agenda for more active participation from African scientists, clinicians, implementers, and policy makers as this moves forward.

**Response:** We agree entirely about the limitations of the roundtable. The reason is that the roundtable was an opportunistic event scheduled to coincide with the Conference on Retroviruses and Opportunistic Infections (CROI), which is held in the United States and is primarily a research meeting. Participants were thus CROI attendees, who come mainly from North America and Europe and are mainly scientists, not implementers. We agree that more active participation from stakeholders in Africa is needed as the preliminary research questions we proposed are developed into studies and evaluations.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 21 August 2020

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**Tom Decroo** 

Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, Belgium

With interest I read “Models of service delivery for optimizing a patient’s first six months on antiretroviral therapy for HIV: an applied research agenda”. The manuscript addresses an important topic and is very well written.

Please find a first comment for a minor revision and a second comment for your consideration.

“Because DSD models were originally conceived as a way to manage rapidly expanding populations of experienced patients who are clinically “stable” on ART”. The first documented DSD model was piloted to serve populations out of reach of the formal health system. Hence, DSD are not only about more efficient provision of care for stable patients, but also about differentiating care provision to meet with the reality of people’s daily life, also for those living in a rural community or those who experience stigma when visiting a health facility.

I agree with the authors that the present facility-based model of care is not providing the best possible care for some patients, illustrated by the relatively high level of attrition during the first 6 months of treatment. Hence, this “gold standard” has its own limitations. Moreover, problems are underestimated as most data only report outcomes among those who sought health facility-based care. Those out of reach, or experiencing stigma, are not included in most study denominators. Given the limitations of the present gold standard there should be room for more drastic modifications than those proposed to test. While I agree that it is meaningful to compare the effect of each of the different components of the conventional facility-based care model with alternative approaches in community-based care, as shown in table 1, I also invite the authors to go one step further. Why not ask the opposite question? How can facility-based activities be adapted to support/complement community embedded and PLHIV network-driven comprehensive HIV care models?

Please also consider adding questions related to self-efficacy and ownership, known drivers of sustained ART adherence. With comprehensive HIV care all activities (testing, ART initiation, early and long term ART) would be planned together with community members and provided within the community, while maintaining a strong link with the health facility. Instead of using criteria for referral from facility-based to DSD, patients with specific needs would be referred to a health facility, while continuing as a member of a social network. Of course, such an approach would not replace the facility-based approach, but complement it, for efficient management of stable patients, but also for those who experience barriers to facility-based care.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**

Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**

Yes

**Is the Open Letter written in accessible language?**

Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**

Yes

**Competing Interests:** No competing interests were disclosed.**Reviewer Expertise:** community-based HIV care**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Author Response 05 Oct 2020

**Sydney Rosen**

Comment: "Because DSD models were originally conceived as a way to manage rapidly expanding populations of experienced patients who are clinically "stable" on ART". The first documented DSD model was piloted to serve populations out of reach of the formal health system. Hence, DSD are not only about more efficient provision of care for stable patients, but also about differentiating care provision to meet with the reality of people's daily life, also for those living in a rural community or those who experience stigma when visiting a health facility.

**Response:** We thank the reviewer for pointing this out. We agree that DSD models have multiple goals.

Comment: Given the limitations of the present gold standard there should be room for more drastic modifications than those proposed to test. While I agree that it is meaningful to compare the effect of each of the different components of the conventional facility-based care model with alternative approaches in community-based care, as shown in table 1, I also invite the authors to go one step further. Why not ask the opposite question? How can facility-based activities be adapted to support/complement community embedded and PLHIV network-driven comprehensive HIV care models?

**Response:** We appreciate the reviewer's suggestion and agree that adapting facility-based activities to support those outside the facility is important. That said, in most countries and settings, primary healthcare facilities remain the core service delivery mechanism of the public health system. While community based models that do not rely on facilities may be effective and sustainable in some communities, it seems likely that public health systems will continue to utilize facilities as the major provider of care for some time to come. Focusing our research questions on how to use facilities to improve service delivery models thus seems practical.

Comment: Please also consider adding questions related to self-efficacy and ownership, known drivers of sustained ART adherence. With comprehensive HIV care all activities

(testing, ART initiation, early and long term ART) would be planned together with community members and provided within the community, while maintaining a strong link with the health facility. Instead of using criteria for referral from facility-based to DSD, patients with specific needs would be referred to a health facility, while continuing as a member of a social network. Of course, such an approach would not replace the facility-based approach, but complement it, for efficient management of stable patients, but also for those who experience barriers to facility-based care.

**Response:** As explained above, we believe that primary healthcare facilities will continue to serve as the core of the public health system in most sub-Saharan countries for the foreseeable future. The reviewer's proposal for an entirely community-based program that uses healthcare facilities only for special needs is ambitious and may offer a solution in some settings. We would certainly be interested in research in this area, but we do not regard it as a priority for the specific question we have asked.

**Competing Interests:** No competing interests were disclosed.