To: ACTG Scientific Agenda Steering Committee

From: Lionel Hilliard, ACTG Global Community Advisory Board Co-Chair
Morénike Giwa Onaiwu, ACTG Global Community Advisory Board Co-Chair
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RE: Closure of A5263

Dear Scientific Agenda Steering Committee (SASC) members:

As current Co-Chairs of the AIDS Clinical Trials Group (ACTG) Global Community Advisory Board (GCAB) and as the Community Scientific Subcommittee (CSS) representative to protocol A5263, we are writing this letter at the prompting of several of our CAB members across the globe who have reached out to us to express their concerns about the status of this protocol. It is our understanding that due to the protocol's failure to accrue as anticipated, SASC will be voting in the very near future - within a few short days - whether the study should be closed. We are aware that our colleagues from the AIDS Malignancy Consortium (AMC)'s International Community Advisory Board have also provided feedback. We thank you in advance for allowing us to address you about this issue.

First, we acknowledge that accrual into this study has been slower than anticipated, and as such SASC has legitimate reason to be concerned - as you would be with any other protocol whose numbers were lower than projected. We are aware that there are expectations that all protocols must meet in a specified time frame in order to achieve credible results. However, as community representatives, we urge you to consider this decision in a holistic manner and to take into account several additional factors beyond the numbers. The numbers tell one story, but as West African author Chimamanda Adichie reminds us, there is danger in relying upon a single story, and a single story is not only untrue, it is incomplete.

However, even within a single story there are substories. Specifically with regard to this protocol, there were unanticipated delays in the protocol activation process at some sites due to factors such as laboratory training, preparedness, and capacity which affected accrual; for a significant length of time only a third of the total sites were open and able to enroll participants.

Accrual into the study has also been affected by the loss of some key sites which had been projected to make up a sizable amount of enrollment. Additionally, there were drug changes that impacted implementation as well due to a worldwide shortage of Doxil and other issues.

All of this is well known to all of you and the protocol team has worked diligently to increase enrollment despite these problems. Though enrollment is still slow, it has improved since the last formal SASC review in 2015 and the protocol team has demonstrated its commitment to addressing enrollment concerns. In addition to working closely with the CSS representative on this study, the team has sought out the community for feedback (presenting on GCAB and Africa CAB Education calls in 2014 and 2017); we believe this indicates that they are willing to collaborate with entities both within the ACTG (i.e. Outreach, Recruitment, and Retention [ORR]) and outside the ACTG to increase enrollment. We believe this responsiveness would be best met with additional support rather than what might be perceived generally as punitive action.

There is no other study quite like this one that focuses on advanced KS internationally. By pooling expertise and resources, the ACTG and the AMC came together to address a high priority health concern faced by some of the most vulnerable members of the global HIV community - Kaposi Sarcoma (KS), the second most common cancer among those living with HIV worldwide. For those of us fortunate enough to reside in the United States and similarly resource privileged settings in the HAART era, KS is a rare occurrence; not only is it not considered a threat to our lives, it is not even something many younger people living with HIV (PLHIV) think much about. However, it is quite different in resource limited settings such as Sub-Saharan Africa and parts of Latin America, where approximately 85% of the world's cases of KS occur and where men, women, and children are proportionately affected.

PLHIV who have KS are ~4-6 times more likely to die than their positive counterparts without KS. The incidence of KS in Sub-Saharan Africa is staggering: an estimated 4 times the total amount of Americans with both breast AND prostate cancer. It is pretty telling that when one reviews the A5263 accrual reports from September 2013 - October 2014 that were emailed to the community, 17% of the people who were screened for the study died before they could be enrolled; another 23% of those screened for the study were ineligible because in addition to being HIV+ and having KS, they also had one or more "active other illnesses" (some of which were life threatening) which prevented them from being enrolled in the study. 40% of those screened were essentially too ill (17% to the point of death) to even be able to benefit from it.

And this is why we implore you to consider more than the "single story" of the low numbers. Again, we don't dispute the fact that, though there have been improvements, frankly, the accrual numbers are disappointing. They are - and because we take our position as partners to the researchers seriously, we won't disregard or ignore that. We think - and we urge - SASC to continue to pay close attention to the numbers and to expect improvement moving forward.

However, we - the global we, not simply "we" who are drafting this letter - believe that this study should remain open longer than November 2017 not only because it deals with an important research question; not only because to our knowledge it is the only open ACTG study whose central focus is opportunistic infection; and not only because there are members of our CABs whom we care for deeply who are participants in this study. We believe it should remain open because at this time we, the ACTG, have an ethical responsibility to see this matter through.

The level of stigma that PLHIV who have KS face is enormous. Some of us remember a similar level of crushing stigma when KS was more common in the US. KS is a visible, identifiable symbol that you are "sick," and/or "dirty," and/or "one of those AIDS people," and/or "cursed." Moreover, on top of the social stigma, KS is painful, and with the current standard of care for KS in resource limited settings even those who survive it are often plagued with discomfort and reduced function, which impacts their overall ability to be self-sufficient, limiting employment prospects and resulting in a suboptimal quality of life.

Everything we've stated above you all know very well; better than we do. There is little, and possibly nothing, that we have said thus far that you haven't heard, or read, or written, or perhaps even seen for yourselves among your own participants and/or clients. Therefore, you know that KS remains a critical issue in the face of HIV in Sub-Saharan Africa.

We strongly believe that stopping such an important trial will do more than merely destroy the hopes of more than the ~200+ individuals who have volunteered themselves for this study. It will also send a resounding message to this region of the world - and to the international community of stakeholders, medical professionals, staff, and others who respect the groundbreaking work of the ACTG - that some people don't truly matter. That is NOT the truth, and we do not want to inadvertently send such a message by prematurely closing this vital study. By extending flexibility and support to A5263 in order to obtain more enrollees and therefore increase statistical relevance, we send the message that in the ACTG, **everyone** matters.

It is our hope that you will find a "creative work around" that will grant A5263 more time to enroll participants through most or all of 2018 while still holding the team accountable for finding ways to boost enrollment where possible. As we have stated previously, we feel that your concern about the enrollment is justified. It cannot be overemphasized that we all have a responsibility to study participants to ensure that our studies will adequately enroll enough individuals to be able to properly answer the research questions. The more participants that the study acquires, the more statistically accurate the information that is discovered will be. However, we do not feel that closing the study is the solution - especially in light of the complicated factors involved in this case.

Please note that we do not make this request lightly; it is only after thorough consultation with and feedback from numerous members of the ACTG community that we decided to address SASC with our concerns. We would not make this request if this was not a topic that we feel strongly about. There have been other studies through the years that the community has rallied behind that have struggled with low enrollment, and when such studies were proposed to close early to accrual, we supported those decisions. Examples from recent years that immediately come to mind are 1) the Promoting Maternal and Infant Survival Everywhere (PROMISE) joint study with the IMPAACT network and 2) A5251.

Both of these protocols addressed important research questions and were highly supported by the community. PROMISE was a global protocol that assessed whether to stop or continue HAART postpartum in treatment naive women living with HIV to enhance infant and maternal health. A5251 examined issues related to adherence-related virologic failure in high risk PLHIV (including women and people of color). Though we supported these studies, we agreed with the ACTG's rationale for closing these studies early and did not dispute the decision to do so.

We are taking a different position in this instance because we believe this case to be different than those scenarios. Also, we believe that though this study has had its challenges, we believe this protocol is worth extending. We believe our Sub-Saharan African and Latin American brothers, sisters, friends, and colleagues to be worth it and we believe this topic to be worth it.

In closing, as the serious nature of this closure cannot be overstated, on behalf of the international ACTG community, we urgently request you to consider allowing protocol A5263 to continue accrual through next year for credible results and for the ethical reasons outlined above.

Furthermore, we support renewed implementation of accrual guidelines for the remainder of 2017 and 2018 to ensure A5263 is able to enroll to at least 80% power for statistical credibility. Your consideration will help bring hope to vulnerable individuals living with this threatening condition in resource constrained Sub-Saharan Africa and elsewhere.

It will also inspire the ACTG community as a whole, regardless of whether KS is epidemic in our region or not, for we are one global community. As Dr. Martin Luther King, Jr. wrote in his renowned letter from a Birmingham Jail, "...whatever affects one of us directly affects all indirectly."

Respectfully,

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