Dear editor,

Thank you for the opportunity to respond to the letter of Breton G and colleagues. We welcome the authors' engagement on the challenge of underuse of second-line antiretroviral treatment, expressing as they do the notion that the *application* of the algorithm can hinder effective patient management.

We do not however disassociate the Viral Load (VL) algorithm itself from the results of its application in the real world, recalling the axiom that "*systems are perfectly designed to achieve the results they get*" this system being an interplay between the prescribed approach and real world factors, giving rise to widespread second-line underuse and significant global morbidity and mortality.

In a similar way to Breton and colleagues, we have observed in practice the situation whereby a modest decline in VL -- after an adherence intervention -- results in procrastination and delayed switch, often with disastrous patient consequences. The current approach may potentiate conservatism and inertia.

Considering the generalizability of our results, pretreatment resistance to NNRTIs in South Africa is estimated to be around 10% (1) with similar findings published for Guinea Bissau (2) and a range of West African countries(3). Indeed given that in these settings advanced disease is seen more frequently than in many Southern African countries (4) there is likely a greater need to ensure prompt switch to second-line. In MSF supported sites in Kinshasa, Democratic Republic of Congo, a simplified switch algorithm is already in practice for patients admitted with advanced HIV (5); a response to the appallingly high mortality and HIV drug resistance levels observed in patients entering hospital with advanced HIV having failed therapy (6).

The authors provide personal data that 50% of patients with VL≥1000 copies/ml re-suppressed after adherence strengthening. Published evidence estimates re-suppression at 20-50%, with limited durability of re-suppression and conflicting data on the efficacy of adherence counselling(7)(8)(9). Closely monitored patients in trials and centres of excellence are not those that suffer the most severe consequences of failure and their staff may be less reliant on public health algorithms, which do not replace tailored care where that can be afforded. We would ask how durable was suppression in those who did suppress in this experience and what happened to those that did not? Furthermore, in table 3 we present a sensitivity analysis illustrating that even if suppression exceeds 40% the difference between the strategies remains similar.

The prescriber's perspective that the authors mention, whereby adherence should be "*sufficiently strengthened*" before proposing second-line should be avoided for the following reasons:

i) There is an implicit assumption in such an approach that all failure arises from non-adherence, whereas much, as mentioned above, is due to transmitted resistance, in which case there may not be at the time point of interest, nor in the period leading up to it, an

adherence issue. ii) Healthcare systems are on dubious ground when they withhold potentially lifesaving therapy from an individual on the basis of what is (in the absence of therapeutic drug levels) a subjective impression of that individual's adherence, or improvement thereof. Such a situation in relation to some other class of therapy such as metformin for diabetes would be unthinkable and the notion that such an approach supports the conservation of therapy, whether at the individual or population level, presumes to sacrifice current health gain for uncertain future benefits, . iii) the interventions we use to strengthen adherence lack robust evidence of effectiveness.

We advocate that adherence interventions should be provided in parallel with the institution of effective therapy; not be a hoop to jump through before receiving it.

The simplified algorithm indeed only applies to EFV based ART. Given the higher genetic barrier to resistance noted, and the differing cost benefit implications involved with a dolutegravir-based 1st line, we feel that differential thresholds will be important to operationalize. In settings with EFV-based 1st line, a rapid shift towards DTG-based second line would allow for significant cost-savings as well as clinical benefits, and, one might hope, an increase in switch to second line.

Changes to guidelines and practice should be based upon a range of evidence and we agree wholeheartedly with the "*need to accompany the current algorithm and any potential modifications with a practical translation corresponding to the realities in the field*." We also agree on the need for contextual adaptations of such approaches. While such work has begun in some centres among some populations, as noted earlier, further work in this regard is indeed greatly needed. In this vein, we wish the authors the greatest success with their working group and guidelines to help ensure that the role of VL for patient benefit can be maximized in their setting.

Your sincerely,

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