particularly in terms of finance, procurement, health information system, lab and clinical human resources capacity building, so that efforts to increase access to viral load can lead to improving patient care and not just informing the third 90%.

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'Let's talk about failure' working group: AMAN C.M.L. (Abidjan), BRETON G. (Bagnolet), DOUOLI S.M. (Abidjan), GAKIMA D. (Bujumbura), GOUESSE Y.P. (Abidjan), GUILAVOGUI F. (Conakry), KAREMANGINO S. (Bujumbura), KAREMERA F. (Bujumbura), MAMANE H. (Conakry), MOUKOKO DOUALLA A.C.M. (Cameroun), SOUMAH M.M. (Conakry), TEMGOUA E.M. (Youndé), ZANA D.K. (Abidjan).

Guillaume Breton[a], Gabrièle Laborde-Balen[b,c], Foromo Guilavogui[d], Saidi Karemangino[e], Daniel K. Zana[f], Edith M. Temgoua[g], Christine Rouzioux[h], Louis Pizarro[a], Roland Tubiana[i], the 'let's talk about failure' working group *[a]Solthis, Bagnolet, [b]IRD UMI 233 TransVIHMI-INSERM U1175, Montpellier University, Montpellier, France, [c]Centre régional de Recherche et de formation à la prise en charge Clinique de Fann, Dakar, Senegal, [d]PNLSH, Conakry, Guinea, [e]PNLS/IST, Bujumbura, Burundi, [f]PNLS, Abidjan, Côte d'Ivoire, [g]CNLS, Yaoundé, Cameroun, [h]Department of Virology, Necker Hospital, and [i]Department of Infectious and Tropical Diseases, Pitié-Salpêtrière Hospital, Paris, France.*

Correspondence to Guillaume Breton, Solthis, Bagnolet, France.
E-mail: guillaume.breton@solthis.org

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HIV viral load algorithm: what are the needs in the field?: authors' response

Thank you for the opportunity to respond to the letter of Breton *et al.* [1]. 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 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 *et al.* [1], we have observed in practice the situation whereby a modest decline in viral load – 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% [2] with similar findings published for Guinea Bissau [3] and a range of West African countries [4]. Indeed, given that in these settings, advanced disease is seen more frequently than in many Southern African countries [5], 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 [6]; a response to the appallingly high mortality and HIV drug resistance levels observed in patients entering hospital with advanced HIV having failed therapy [7].

Breton *et al.* [1] provide personal data showing that 50% of patients with viral load at least 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 [8–10]. 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 mentioned by Breton *et al.* [1], whereby adherence should be 'sufficiently strengthened' before proposing second-line should be avoided for the following reasons: there is an implicit assumption in such an approach that all failure arises from nonadherence, whereas much, as mentioned above, is because of 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. 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. 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 efavirenz-based antiretroviral therapy (ART). Given the higher genetic barrier to resistance noted, and the differing cost benefit implications involved with a dolutegravir-based first-line, we feel that differential thresholds will be important to operationalize. In settings with efavirenz-based first-line, a rapid shift towards dolutegravir-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. Although 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 Breton *et al.* [1] the greatest success with their working group and guidelines to help ensure that the role of viral load for patient benefit can be maximized in their setting.

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Amir Shroufi[a], Gilles Van Cutsem[a], Valentina Cambiano[b], Loveleen Bansi-Matharu[b], Kristal Duncan[a], Richard A. Murphy[c], David Maman[a] and Andrew Phillips[b], *[a]Médecins Sans Frontières, Cape Town, South Africa, [b]Institute for Global Health, UCL, London, UK, and [c]Division of Infectious Diseases, Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, California, USA.*

Correspondence to Amir Shroufi, MSF, Cape Town, South Africa.
E-mail: amir.shroufi@doctors.org.uk

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Letter to the editor re: Cabrera *et al.*, 2019 'The antagonism of folate receptor by dolutegravir: developmental toxicity reduction by supplemental folic acid'

We have read the publication by Cabrera *et al.* [1] with interest and would like to share some thoughts with the readership. The aims of this letter are to clarify rodent embryo-fetal data used to support dolutegravir registration; contextualize the zebrafish obervations made by Cabrera *et al.* [1]; and provide an alternative interpretation of folate receptor α (FRα) antagonism results using established extrapolation of this type of in vitro inhibition data to human.

Cabrera *et al.* [1] cite a single occurrence of cranioschisis in rabbits given dolutegravir. In studies conducted for dolutegravir registration, one cranioschisis was observed at the lowest dose tested, and there were no other rabbit fetuses with NTDs at dolutegravir exposures up to 17-fold higher (1 NTD in 552 rabbit fetal exposures, 0.18% rabbit NTD rate). This observation was not considered related to dolutegravir exposure, because there were no NTD findings at higher doses and exposures, and the NTD rate was consistent with the background NTD rate. All the rodent embryo-fetal safety studies conducted for dolutegravir registration demonstrated one NTD in 2028 rodent fetal exposures (0.05% overall rodent NTD rate). As in humans (background NTD rate ∼0.1%) [2], it is common to observe background findings of NTDs in large rabbit and rat embryo-fetal safety studies [3,4].

Cabrera *et al.* [1] reported zebrafish developmental toxicities for dolutegravir, which were mitigated by folic acid. The finding of toxicity in zebrafish is not surprising as dolutegravir is known to be hazardous to aquatic life [5] at concentrations similar to those tested by Cabrera *et al.* [1]. Furthermore, the mammalian embryo is at least 1000-fold more sensitive than a zebrafish embryo to antifolates such as methotrexate [6,7]. The zebrafish data reported by Cabrera *et al.* [1] suggest that dolutegravir is as potent as methotrexate in antagonizing folate metabolism/transport, which is not substantiated in the mammalian embryo based on data in rats and rabbits, and also in the rat whole embryo culture, where dolutegravir incubated at double the clinical maximal concentration was not embryo-toxic [8].

The discrepancy in the response of fish embryo compared to mammalian embryo is also not due to differences in the developmentally sensitive exposure windows. All stages of embryo development (zygote, blastula, preimplantation and pregastrulation embryo, and implantation periods) have been evaluated in the studies that were conducted to support dolutegravir registration (Prescribing Information).

Cabrera *et al.* [1] concluded that dolutegravir is a FRα antagonist at clinically relevant concentrations based on comparison of in-vitro potency to total plasma concentrations of highly (>98.9%) plasma protein bound dolutegravir. The accepted scientific practice is to relate these types of in-vitro potencies to unbound drug concentrations, as plasma protein bound drug is not available to interact with the receptor [9]. In fact, Cabrera *et al.* [1] did not observe significant concentration-dependent FRα antagonism when 4% albumin was added to the assay to mimic clinical unbound dolutegravir concentrations (Cabrera *et al.* [1], Supplemental Fig. 2), consistent with two independent studies that reported no FRα inhibition at clinical unbound dolutegravir concentrations [10,11].

In conclusion, it is important to consider an alternative interpretation of the results of the study by Cabrera *et al.* [1] in the context of what has been reported in other studies. While there is no doubt that folate supplementation reduces the general risk of NTDs and should be made available for all women of child-bearing potential, current dolutegravir data suggest this may not be the answer, should the preliminary signal of elevated NTD risk persist as additional human data become available. Furthermore, the use of an aquatic model to study dolutegravir is not ideal, given the nonspecific toxicity that has been noted in fish exposed to dolutegravir as part of the environmental safety assessment.

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Elizabeth H. Romach[a], Dinesh Stanislaus[b] and Maciej J. Zamek-Gliszczynski[b], *[a]ViiV Healthcare, RTP, North Carolina, and [b]GlaxoSmithKline, Collegeville, Pennsylvania, USA.*