activation. The effect of maraviroc intensification has also been modest and variable, with several trials showing no change in HIV persistence measures.1,11,12

It is difficult to compare these intensification studies. Many had small sample sizes or had varying participant demographics, ART regimens and timing, or DNA and RNA quantification methods. Furthermore, newer generation integrase inhibitors with once daily dosing schedules and favourable resistance barriers, such as dolutegravir, are supplanting the use of raltegravir in many clinics. In the current placebo-controlled trial of dolutegravir intensification, Rasmussen and colleagues1 noted no significant differences in circulating cell-associated HIV-2-LTR circles, HIV DNA, unspliced RNA, or low-level residual plasma RNA between dolutegravir intensification or placebo groups. Of note, dolutegravir intensification was associated with a paradoxical lower level of 2-LTR circles at a single timepoint in a regression analysis compared with placebo, but this was transient and not recorded in primary outcome repeat measures analyses. No major differences in markers of immune activation were noted between groups.1

Rasmussen and colleagues1 provide rationale for the discrepancy between their dolutegravir intensification investigation and the previous studies of raltegravir. For example, most participants in the dolutegravir study were on a non-nucleoside reverse transcriptase inhibitor-based regimen, and in contrast to raltegravir, dolutegravir concentrations in the gut are only a fraction of those in the blood and might not have had as potent of an effect in tissue. Furthermore, the dolutegravir study was powered to detect a three-fold change in 2-LTR circle counts and small changes might have been missed.

Irrespective of one’s view on residual HIV replication in the setting of suppressive ART, three-drug combination ART continues to be the mainstay of treatment, with the exception of certain scenarios such treatment-experienced individuals with known or potential resistance mutations. Overall, there is little clinical momentum to intensify existing regimens with additional drug classes. The study by Rasmussen and colleagues1 reinforces this notion. However, one suspects that pending addition of another antiretroviral drug class, a new round of intensification studies will commence.

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Nutritional support to reduce mortality in patients with HIV?

Despite increased access to antiretroviral therapy (ART) in patients with HIV, mortality is very high during the early months of treatment.1 Immunosuppression and undernutrition, presenting as either low body mass index (BMI) or micronutrient deficiency, are among the key risk factors for increased mortality.2 Several clinical trials have investigated the role of micronutrient and macronutrient supplementation on HIV-related
treatment outcomes including mortality, but many
have shown no effects or only modest beneficial
effects.3,4

In The Lancet HIV, Jane Mallewa and colleagues5
report the results of a large multicentre clinical trial in
HIV clinics in Kenya, Malawi, Uganda, and Zimbabwe
in which the researchers tested whether ready-to-
use supplementary food (RUSF) reduced mortality
in severely immunocompromised patients with HIV
starting ART. The investigators randomly assigned
897 adults and children aged at least 5 years to peanut-
based RUSF (1000 kcal per day) and 908 to no-RUSF
(control) for 12 weeks and followed up for 48 weeks.
In both groups, individuals received supplementation
with ready-to-use therapeutic food only when severely
malnourished (BMI <16–18 kg/m² or BMI-for-age
Z scores <–3 for children). At 24 weeks, there was no
effect of the intervention on the primary outcome of
mortality (hazard ratio 1·05, 95% CI 0·79–1·40, log-rank
p=0·75). However, the RUSF group had greater gains
than the control group of weight, BMI, and mid-upper-
arm circumference. These findings echo those from
three previous large trials: NUSTART, a trial in Tanzania
and Zambia that showed vitamin and mineral
supplementation had no effect on mortality at 12 weeks
after ART initiation, but was associated with an increase
in CD4 cell counts;6 a Malawian trial testing 14 weeks of
RUSF versus a corn and soy blend for undernourished
patients starting ART, which led to increased weight and
lean mass but had no effect on mortality;7 and a trial of
a high-dose multivitamin supplement for 24 months
in patients starting ART in Tanzania, which showed no
effect on disease progression or mortality.8

The absence of any effect on survival with RUSF2
could be a result of several factors, including inadequate
composition and duration of the intervention. However,
we believe that one of the most likely reasons is that
nutritional supplementation doesn’t necessarily achieve
its aim if given during illness. RUSF fortified with
micronutrients could theoretically mediate mortality
reduction by increasing lean mass and immunity and
modulating metabolic functions. Although there was
a beneficial effect on lean mass in this trial, this benefit
might not have been enough to increase survival and
this inadequate lean mass, coupled with the absence
of effect on CD4 cell counts could have contributed to
the overall absence of effect on mortality. Even with
supplemental micronutrients and macronutrients in
the intervention group, the acute phase response to
infection at the beginning of ART might have changed
nutrient metabolism and hormonal controls rendering
adequate tissue deposition as well as immunity
recovery impossible. In patients with tuberculosis,
a population with inflammation as severe as that in
HIV-infected patients, nutritional supplementation did
not lead to full nutritional recovery because of impaired
anabolism during treatment.10,11 In Ethiopia, RUSF with
micronutrients at a concentration of one reference
nutrient intake, compared with unsupplemented HIV-
infected patients, was associated with a considerable
increase in lean mass in a subgroup of patients with
viral suppression,12 but not in those without viral
suppression, suggesting that reduction of inflammation
might have contributed to the beneficial effects in the
viral-suppressed subgroup. Thus, similar mechanisms
might underlie the results of Mallewa and colleagues’
trial1 and previous trials.6–8

In the light of these findings, should nutritional
supplementation continue to be encouraged in patients
starting ART? The answer is yes, it is crucial that we
continue to encourage nutritional support because it
might increase lean mass, hasten physical and functional
recovery, and improve work capacity and quality of
life13—important attributes in sustaining livelihoods
of HIV-infected patients in resource-limited settings.
However, two key questions are which patients should
receive supplements and when. The evidence from
Mallewa and colleagues’ study5 suggests that low
CD4 cell counts should not be used as an indicator for
supplementation, while findings from other studies
indicate that low BMI could be used as a marker.12 Future
studies should investigate the appropriate timing for
initiating nutritional support in HIV-infected patients
when inflammation has reduced, to help provide a
scientific basis for further trials of nutritional interventions
in improving health of HIV-infected patients.

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HIV incidence and scale-up of prevention in western Kenya

As the global scientific community grapples with how to achieve HIV elimination in countries where the infection is endemic, in their Article in The Lancet HIV, Borgdorff and colleagues report encouraging results. Ever since HIV preventive efficacy of both voluntary medical male circumcision (VMMC) and antiretroviral therapy (ART) were reported, researchers have been increasingly optimistic that scale-up of these interventions in a combination strategy might lead to population epidemic control.1,2 Borgdorff and colleagues aimed to establish the trends in HIV infection prevalence and incidence between 2011 and 2016 in Siaya county, a high HIV burden area in western Kenya. From 2011, ART was prescribed to HIV-infected individuals with CD4 counts of less than 350 cells per µL (WHO stage 1 or 2 disease), and from 2014, to HIV-infected individuals with CD4 counts less than 500 cells per µL. The HIV test and start programme strategy were rolled out in 2016. Borgdorff and colleagues did secondary analysis on programme data and HIV test results collected from three population-based HIV surveys (2011, 2012, and 2016) among participants aged 15–64 years.

HIV prevalence declined by one-third in participants aged 15–34 years, but did not change in participants aged 15–64 years. HIV incidence declined from 11.1 (95% CI 9.1–13.1) to 5.7 (4.6–6.9) per 1000 person-years. Although the declines did not reach the estimated threshold for HIV elimination of one case per 1000 person-years,4,5 the findings indicate positive progress and that elimination is possible, especially if the results are generalisable in contexts where HIV is endemic. Efforts need to be intensified to accelerate and magnify the positive trends, and then sustain these effects over time, even with possible declining international financial support.

Considered in the context of empirical findings of the effects of VMMC and ART on HIV incidence,6,9 the temporal association between rapid scale-up of the combination strategy for HIV prevention and population-level declines in the incidence of HIV infection lends support to a possible cause-and-effect relationship between the two.

These findings are based on programmatic data in a real-world setting in Kenya. They are comparable with the 42% decline in HIV incidence during a 10 year scale-up (up to 2016) of HIV combination prevention strategy that included VMMC, ART, and voluntary HIV testing and counselling in rural Rakai district, Uganda, among participants aged 15–49 years in a population longitudinal cohort study reported from the Rakai Health Sciences Program.10