activation. The effect of maraviroc intensification has also been modest and variable, with several trials showing no change in HIV persistence measures.[4, 11–13]

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 colleagues[3] 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.[3]

Rasmussen and colleagues[3] 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 countrs 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 colleagues[3] reinforces this notion. However, one suspects that pending addition of another antiretroviral drug class, a new round of intensification studies will commence.

Timothy J Henrich
Division of Experimental Medicine, University of California, San Francisco, San Francisco, CA 94110, USA
timothy.henrich@ucsf.edu

I declare no competing interests.

1 van Zyl G, Bale MJ, Kearney MF. HIV evolution and diversity in ART-treated patients. *Retrovirology* 2018; **15:** 14.
2 Hunt PW, Shulman NS, Hayes TL, et al. The immunologic effects of maraviroc intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. *Blood* 2013; **121:** 4635–46.
3 Rasmussen TA, McMahon JH, Chang JJ, et al. The effect of antiretroviral intensification with dolutegravir on residual virus replication in HIV-infected individuals: a randomised, placebo-controlled, double-blind trial. *Lancet HIV* 2018; published online April 9. http://dx.doi.org/10.1016/S2352-3018(18)30040-7
4 Ananworanich J, Chomont N, Fletcher JL, et al. Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification. *J Virus Erad* 2015; **1:** 116–22.
5 Hatano H, Strain MC, Scherzer R, et al. Increase in 2-long terminal repeat circles and decrease in D-dimer after raltegravir intensification in patients with treated HIV infection: a randomized, placebo-controlled trial. *J Infect Dis* 2013; **208:** 1436–42.
6 Vallejo A, Gutierrez C, Hernandez-Novoa B, et al. The effect of intensification with raltegravir on the HIV-1 reservoir of latently infected memory CD4 T cells in suppressed patients. *AIDS* 2012; **26:** 1885–94.
7 Gandhi RT, Coombs RW, Chan ES, et al. No effect of raltegravir intensification on viral replication markers in the blood of HIV-1-infected patients receiving antiretroviral therapy. *J Acquir Immune Defic Syndr* 2012; **59:** 229–35.
8 Puertas MC, Massanella M, Llibre JM, et al. Intensification of a raltegravir-based regimen with maraviroc in early HIV-1 infection. *AIDS* 2014; **28:** 325–34.
9 Buzon MJ, Massanella M, Llibre JM, et al. HIV-1 replication and immune dynamics are affected by raltegravir intensification of HAART-suppressed subjects. *Nat Med* 2010; **16:** 460–65.
10 Martinez-Picado J, Zurakowski R, Buzon MJ, Stevenson M. Episomal HIV-1 DNA and its relationship to other markers of HIV-1 persistence. *Retrovirology* 2018; **15:** 15.
11 Cillo AR, Hilldorfer BB, Lalama CM, et al. Virologic and immunologic effects of adding maraviroc to suppressive antiretroviral therapy in individuals with suboptimal CD4+ T-cell recovery. *AIDS* 2015; **29:** 2121–29.
12 Gutierrez C, Hernandez-Novoa B, Vallejo A, Serrano-Villar S, Abad-Fernandez M, Madrid N, et al. Dynamics of the HIV-1 latent reservoir after discontinuation of the intensification of antiretroviral treatment: results of two clinical trials. *AIDS* 2013; **27:** 2081–88.
13 Wilkin TJ, Lalama CM, McKinnon J, et al. A pilot trial of adding maraviroc to suppressive antiretroviral therapy for suboptimal CD4(+) T-cell recovery despite sustained virologic suppression: ACTG A5256. *J Infect Dis* 2012; **206:** 534–42.

Nutritional support to reduce mortality in patients with HIV?

Published Online
April 10, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30047-X
See Articles page e231

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 colleagues[5] 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 RUSF[5] 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[9]. 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' trial[5] 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 life[7,12,13]—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' study[5] 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.[7,12] 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.

**George PrayGod, Henrik Friis, Suzanne Filteau*
Mwanza Research Centre, National Institute for Medical Research, Box 1462, Mwanza, Tanzania (GP); Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark (HF); and Department of Population Health, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK (SF)
gpraygod@yahoo.com

HF reports research grants from Arla Food for Health and Nutriset. GP and SF declare no competing interests.

1 Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008; **22:** 1897–908.
2 Woodd SL, Kelly P, Koethe JR, et al. Risk factors for mortality among malnourished HIV-infected adults eligible for antiretroviral therapy. *BMC Infect Dis* 2016; **16:** 562.
3 Grobler L, Siegfried N, Visser ME, Mahlungulu SS, Volmink J. Nutritional interventions for reducing morbidity and mortality in people with HIV. *Cochrane Database Syst Rev* 2013; **2:** CD004536.
4 Visser ME, Durao S, Sinclair D, Irlam JH, Siegfried N. Micronutrient supplementation in adults with HIV infection. *Cochrane Database Syst Rev* 2017; **5:** CD003650.
5 Mallewa J, Szubert AJ, Mugyenyi P, et al. Effect of ready-to-use supplementary food on mortality in severely immunocompromised HIV-infected individuals in Africa initiating antiretroviral therapy (REALITY): an open-label, parallel-group, randomised controlled trial. *Lancet HIV* 2018; published online April 10. http://dx.doi.org/10.1016/S2352-3018(18)30038-9.
6 Team NS, Filteau S, PrayGod G, et al. Effects on mortality of a nutritional intervention for malnourished HIV-infected adults referred for antiretroviral therapy: a randomised controlled trial. *BMC Med* 2015; **13:** 17.
7 Ndekha MJ, van Oosterhout JJ, Zijlstra EE, Manary M, Saloojee H, Manary MJ. Supplementary feeding with either ready-to-use fortified spread or corn-soy blend in wasted adults starting antiretroviral therapy in Malawi: randomised, investigator blinded, controlled trial. *BMJ* 2009; **338:** b1867.
8 Isanaka S, Mugusi F, Hawkins C, et al. Effect of high-dose vs standard-dose multivitamin supplementation at the initiation of HAART on HIV disease progression and mortality in Tanzania: a randomized controlled trial. *JAMA* 2012; **308:** 1535–44.
9 PrayGod G, Blevins M, Woodd S, et al. A longitudinal study of systemic inflammation and recovery of lean body mass among malnourished HIV-infected adults starting antiretroviral therapy in Tanzania and Zambia. *Eur J Clin Nutr* 2016; **70:** 499–504.
10 Macallan DC, McNurlan MA, Kurpad AV, et al. Whole body protein metabolism in human pulmonary tuberculosis and undernutrition: evidence for anabolic block in tuberculosis. *Clin Sci (Lond)* 1998; **94:** 321–31.
11 Schwenk A, Hodgson L, Wright A, et al. Nutrient partitioning during treatment of tuberculosis: gain in body fat mass but not in protein mass. *Am J Clin Nutr* 2004; **79:** 1006–12.
12 Olsen MF, Abdissa A, Kaestel P, et al. Effects of nutritional supplementation for HIV patients starting antiretroviral treatment: randomised controlled trial in Ethiopia. *BMJ* 2014; **348:** g3187.
13 Tesfaye M, Kaestel P, Olsen MF, et al. The effect of nutritional supplementation on quality of life in people living with HIV: a randomised controlled trial. *Trop Med Int Health* 2016; **21:** 735–42.

HIV incidence and scale-up of prevention in western Kenya

Published Online
April 9, 2018
http://dx.doi.org/10.1016/S2352-3018(18)30042-0

See Articles page e241

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[1] 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.[2,3] 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 35xlls 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]