

## The LATTE study: a provocative brew



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Published Online  
July 20, 2015

[http://dx.doi.org/10.1016/S1473-3099\(15\)00224-8](http://dx.doi.org/10.1016/S1473-3099(15)00224-8)

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The history of the development of combination anti-retroviral therapy (ART) has shaped our understanding of the principles governing ART's construction and use. It was at the 11th International AIDS Conference held 19 years ago in Vancouver, BC, Canada, that the results of the first ART studies assessing combination therapy using two nucleoside analogue reverse transcriptase inhibitors (NRTIs) plus a protease inhibitor were reported.<sup>1</sup> This was followed shortly after by reports of successful combination therapy using a non-NRTI plus two NRTIs.<sup>2</sup> This sequence of events founded the principle that triple therapy was the minimum requirement for control and maintenance of long-term virological suppression. This principle was reinforced by the early unsuccessful attempts to use an induction–maintenance strategy (using two drugs from either one or two ART classes) as a means to streamline long-term HIV management.<sup>3,4</sup>

Despite that general understanding, some investigators have continued to pursue alternative strategies that challenge the dominant triple-therapy framework, particularly combination ART that does not include nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs). This approach was rationalised on the basis that the major adverse events and toxic effects associated with combination ART have been most closely linked to the N(t)RTI drug class, and that ART is a lifelong commitment that requires the parsimonious use of agents in a way that should preserve future effective combination therapy for decades.

The DMP-006 study<sup>5</sup> was the first to show the improved efficacy of an efavirenz-anchored strategy over a protease-inhibitor-anchored strategy. Less well remembered is that the results of DMP-006 also showed that a strategy of dual ART using indinavir three times daily (unboosted) plus efavirenz once daily was superior to indinavir three times daily plus zidovudine and lamivudine. 10 years later the ACTG 5142 study,<sup>6</sup> with a similar design to DMP-006 but with boosted lopinavir instead of unboosted indinavir, showed that a regimen with a boosted protease inhibitor plus two N(t)RTIs was inferior to the efavirenz plus two N(t)RTI regimen; the result for the boosted lamivudine plus efavirenz regimen was consistent with non-inferiority compared with the efavirenz plus two N(t)RTI regimen.

With the approval over the past 8 years of drugs in new and existing classes, opportunities have arisen

for trials of alternative dual therapy regimens and induction–maintenance strategies. The most recent of these have suggested that dual therapy might be non-inferior to conventional triple therapy in either first-line or second-line therapy.<sup>7–10</sup> Results of two studies of triple induction, dual maintenance ART suggest a role for this strategy to avoid toxic effects associated with abacavir and tenofovir.<sup>11,12</sup> However, at least in patients naive to ART, findings of no study have been convincing enough to recommend N(t)RTI-sparing ART as either initial or maintenance therapy alongside standard ART.

In *The Lancet Infectious Diseases*, David Margolis and colleagues<sup>13</sup> present the results of the phase 2, dose-ranging LATTE trial in which they studied cabotegravir (a longacting analogue of dolutegravir) combined with rilpivirine as a maintenance strategy for patients with successful virological suppression after 24 weeks of induction with conventional triple therapy.<sup>13</sup> At baseline, participants were randomly assigned to receive one of three separate doses of cabotegravir (10 mg, 30 mg, or 60 mg) plus abacavir-lamivudine or tenofovir-emtricitabine, or to efavirenz 600 mg plus abacavir-lamivudine or tenofovir-emtricitabine. Participants with a viral load of fewer than 50 copies per mL at week 24 in the cabotegravir groups ceased background N(t)RTIs and continued with dual maintenance therapy of cabotegravir plus rilpivirine 25 mg.

The overall result was impressive. Of 243 patients in the primary analysis, 149 (82%) of 181 patients who received cabotegravir plus rilpivirine during maintenance had a viral load of fewer than 50 copies per mL after 24 weeks of maintenance therapy, compared with 44 (71%) of 62 participants who received 48 weeks of efavirenz plus two N(t)RTIs. At week 96 (after 72 weeks of maintenance therapy) this difference was sustained: 137 patients (76%) receiving dual maintenance therapy had a viral load of fewer than 50 copies per mL compared with 39 (63%) of those receiving conventional efavirenz plus two N(t)RTI triple therapy.

Although this study is a typical phase 2 study—ie, it is not powered for definitive conclusions about the relative performance of the experimental strategy and regimen—its results are nonetheless radical and provocative. They challenge the notion that dual therapy is not a realistic option compared with triple therapy. They also challenge

the notion that if dual therapy is an option, it must include a robust agent such as a boosted protease inhibitor. Moreover, they challenge the notion that an induction-maintenance strategy won't be effective if it uses only two drugs.

Intriguingly, this study will not go on to a phase 3 trial examining the selected cabotegravir 30 mg dose plus rilpivirine 25 mg as oral combination therapy. Both drugs have long pharmacokinetic half-lives and are amenable to nanosuspension and intramuscular injection. The LATTE study was used to establish the proof of principle that this dual therapy combination is effective. The LATTE-2 trial—currently in progress—is studying the use of longacting intramuscular cabotegravir 30 mg plus longacting intramuscular rilpivirine 25 mg as the first all injectable two-drug regimen. However, the two pharmaceutical companies responsible for the manufacture of dolutegravir and rilpivirine have announced both an agreement to coformulate these drugs into one tablet (with a total dose of active pharmaceutical ingredients of only 75 mg) and a series of phase 3 studies to assess the clinical use of this oral two-drug alternative as a fixed-dose combination.

The LATTE study might therefore herald not only the beginning of a new era of longacting intramuscular injection as an option for long-term HIV management, but also the dawn of an effective and well tolerated two-drug N(t)RTI-sparing and protease-inhibitor-sparing single tablet regimen for long-term oral ART. The phase 3 study results of both will be awaited with great anticipation.

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MAB has received honoraria for services rendered to the following pharmaceutical companies as a member of HIV advisory boards and/or for preparation of educational materials: AbbVie, Boehringer-Ingelheim, Bristol-Myers Squibb, Gilead, Janssen-Cilag, Merck, and ViiV Healthcare. MAB has received research grant

funding from AbbVie, Merck, and Gilead Sciences. DAC has received grants and personal fees from ViiV Healthcare, Gilead, MSD, and AbbVie.

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## Use of low dose rVSV-ZEBOV: safety issues in a Swiss cohort



Accelerated development of a safe and effective vaccine to prevent Ebola virus disease (EVD) is needed for those at risk of infection and could be used to curtail current and future outbreaks.

In *The Lancet Infectious Diseases*, Angela Huttner and colleagues<sup>1</sup> report the results of a phase 1/2 randomised

placebo-controlled trial assessing the safety and immunogenicity of a replication-competent recombinant vesicular stomatitis virus-based candidate vaccine (rVSV-ZEBOV) expressing the Zaire Ebola virus glycoprotein in healthy adults. Two recent reports describing preliminary phase 1 trial data for this vaccine<sup>2,3</sup> have included

Published Online  
August 4, 2015  
[http://dx.doi.org/10.1016/S1473-3099\(15\)00222-4](http://dx.doi.org/10.1016/S1473-3099(15)00222-4)  
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