Body composition and metabolic outcomes after 96 weeks of treatment with ritonavir-boosted lopinavir plus either nucleoside or nucleotide reverse transcriptase inhibitors or raltegravir in patients with HIV with virological failure of a standard first-line antiretroviral therapy regimen: a substudy of the randomised, open-label, non-inferiority SECOND-LINE study

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Summary

Background Lipoatrophy is one of the most feared complications associated with the use of nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs). We aimed to assess soft-tissue changes in participants with HIV who had virological failure of a first-line antiretroviral (ART) regimen containing a non-nucleoside reverse transcriptase inhibitor plus two N[t]RTIs and were randomly assigned to receive a second-line regimen containing a boosted protease inhibitor given with either N[t]RTIs or raltegravir.

Methods Of the 37 sites that participated in the randomised, open-label, non-inferiority SECOND-LINE study, eight sites from five countries (Argentina, India, Malaysia, South Africa, and Thailand) participated in the body composition substudy. All sites had a dual energy x-ray absorptiometry (DXA) scanner and all participants enrolled in SECOND-LINE were eligible for inclusion in the substudy. Participants were randomly assigned (1:1), via a computer-generated allocation schedule, to receive either ritonavir-boosted lopinavir plus raltegravir (raltegravir group) or ritonavir-boosted lopinavir plus two or three N[t]RTIs (N[t]RTI group). Randomisation was stratified by site and screening HIV-1 RNA. Participants and investigators were not masked to group assignment, but allocation was concealed until after interventions were assigned. DXA scans were done at weeks 0, 48, and 96. The primary endpoint was mean percentage and absolute change in peripheral limb fat from baseline to week 96. We did intention-to-treatment analyses of available data. This substudy is registered with ClinicalTrials.gov, number NCT01513122.

Findings Between Aug 1, 2010, and July 10, 2011, we recruited 211 participants into the substudy. The intention-to-treat population comprised 102 participants in the N[t]RTI group and 108 participants in the raltegravir group, of whom 91 and 105 participants, respectively, reached 96 weeks. Mean percentage change in limb fat from baseline to week 96 was 16·8% (SD 32·6) in the N[t]RTI group and 28·0% (37·6) in the raltegravir group (mean difference 10·2%, 95% CI 0·1–20·4; p=0·048). Mean absolute change was 1·04 kg (SD 2·29) in the N[t]RTI group and 1·81 kg (2·50) in the raltegravir group (mean difference 0·6, 95% CI –0·1 to 1·3; p=0·10).

Interpretation Our findings suggest that for people with virological failure of a first-line regimen containing efavirenz plus tenofovir and lamivudine or emtricitabine, the WHO-recommended switch to a ritonavir-boosted protease inhibitor plus zidovudine (a thymidine analogue nucleoside reverse transcriptase inhibitor) and lamivudine might come at the cost of peripheral lipoatrophy. Further study could help to define specific groups of people who might benefit from a switch to an N[t]RTI-sparing second-line ART regimen.

Introduction Adverse effects associated with treatment of HIV infection include changes in body composition, dyslipidaemia, insulin resistance, type 2 diabetes, and vascular endothelial dysfunction. A concern is that these comorbidities will shorten the life expectancy of people living with HIV. Findings from several studies suggest that people living with HIV have a greater burden and an earlier onset of comorbidities than do their HIV-negative peers.1 Whether this difference relates to an increased prevalence of behaviours and risks associated with cardiovascular disease in people

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Research in context

Evidence before the study
To the best of our knowledge, no studies to date have investigated and reported body composition changes in patients receiving second-line antiretroviral therapy (ART). In 2010, a Cochrane review reported that little evidence existed with which to select second-line ART for people with virological failure of WHO-recommended first-line ART. In the past 3 years, at least four international, multicentre, randomised controlled trials have been published, with an aim to provide high-quality evidence to optimise the management of this patient population. The SECOND-LINE study examined a WHO-recommended strategy of switching to ritonavir-boosted lopinavir plus two or three nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs) versus an N[t]RTI-sparing strategy of ritonavir-boosted lopinavir and raltegravir. We nested a dual energy X-ray absorptiometry (DXA) substudy within the parent study to examine the comparative changes in soft tissue over 96 weeks.

Added value of the study
One concern about the recycling of drugs from the N[t]RTI class for use in second-line ART regimens is that people might develop toxicities associated with the N[t]RTI drug class. One of the most feared complications is the development of lipoatrophy—a disfiguring disorder closely associated with the thymidine analogue nucleoside reverse transcriptase inhibitor (NRTI; eg, zidovudine and stavudine). Lipoatrophy has been associated with negative consequences, including stigma and poor ART adherence. Findings from our substudy suggest that people exposed to zidovudine in second-line ART are less likely to have limb fat gain than those receiving an N[t]RTI-sparing regimen. Multivariate analysis suggested that African women are more likely to lose peripheral fat than are Asian women, and that people with more peripheral fat at treatment initiation are more likely to lose peripheral fat during treatment. We recorded a weak association between duration of thymidine analogue use and peripheral fat loss.

Implications of all the available evidence
Although all trials so far have supported the WHO recommendation to switch to N[t]RTI-containing second-line ART, N[t]RTI-sparing regimens offer non-inferior efficacy and safety. This study suggests that a possible advantage of N[t]RTI sparing is improved peripheral fat gain after a switch from N[t]RTI therapies and avoidance of lipoatrophy in people exposed to a thymidine analogue NRTI. Further study could help to define specific groups of people who might benefit from a switch to N[t]RTI-sparing second-line ART.

Methods

Study design and participants
Of the 37 sites that participated in the randomised, open-label, non-inferiority SECOND-LINE study, eight sites from five countries (Argentina, India, Malaysia, South Africa, and Thailand) participated in the body composition substudy and were analysed as a subgroup of the parent SECOND-LINE study. These sites had access to a dual energy X-ray absorptiometry (DXA) scanner. The substudy was approved by Human Research Ethics Committees at each site. All participants provided written informed consent.

Randomisation and masking
Participants were randomly assigned (1:1), via a computer-generated allocation schedule, to receive ritonavir-boosted lopinavir plus raltegravir (raltegravir group) or ritonavir-boosted lopinavir plus two or three N[t]RTIs (N[t]RTI group). Randomisation was stratified by site and screening HIV-1 RNA. The study was open label, with no masking of participants or investigators, but allocation was concealed until after interventions were assigned.

Procedures
Ritonavir-boosted lopinavir (ritonavir 50 mg, lopinavir 200 mg) could be taken as two tablets twice daily or four tablets once daily at the discretion of the local treating physician; selection of the N[t]RTI component of living with HIV or to increased levels of immune activation despite sustained virological suppression is contested. Whether the development of new classes and new drugs in old classes of antiretroviral therapy (ART) is associated with lesser contributions to cardiovascular risk is also unclear. Lipoatrophy is generally agreed to be most closely associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs), in particular the thymidine analogues (eg, stavudine and zidovudine). Results from a randomised controlled trial suggest that lipohypertrophy as a distinct manifestation of the HIV lipodystrophy syndrome might simply reflect weight gain associated with a return to health, and not an HIV-related or ART-related toxic effect.

Identification of low-toxicity treatment regimens is one of various strategies that aim to combat the adverse effects of combination ART. In this substudy of the SECOND-LINE study, we investigated the effects on body composition of a conventional WHO-recommended second-line ART regimen containing ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors (N[t]RTIs) versus an N[t]RTI-sparing regimen of ritonavir-boosted lopinavir plus raltegravir in participants with HIV with virological failure of a first-line ART regimen. We postulated that the N[t]RTI-sparing strategy would result in greater restoration of limb fat than would conventional combination ART.
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