

1 **Raltegravir in second-line ART in resource-limited settings**

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7 Concerns about nucleoside reverse-transcriptase inhibitor (NRTI) resistance and toxicity are driving a
8 search for NRTI-sparing second-line regimens for HIV. Resistant virus strains can develop when HIV
9 replicates while a person is on antiretroviral therapy (ART). Frequent monitoring of HIV RNA viral load
10 can detect virological failure early and allows timely switching, which prevents accumulation of viral
11 resistance.¹ Although WHO recommends routine viral load monitoring of ART,² many low-income and
12 middle-income countries have not progressed far in implementation and access remains insufficient.³
13 In settings without access to routine viral load monitoring, clinical or immunological criteria are used
14 to monitor patients.¹ These criteria poorly predict virological failure⁴ and treatment failure is often
15 detected late.¹ NRTI resistance is common among patients with treatment failure, especially among
16 those without access to routine viral load monitoring.⁵

17 NRTI resistance is common, but does it compromise the effectiveness of NRTIs in second-line therapy?
18 In *The Lancet HIV*, Alberto La Rosa and colleagues⁶ present results from the SELECT study, a
19 randomised controlled, multicentre, phase 3, non-inferiority trial that compared WHO-
20 recommended² standard second-line regimen of ritonavir-boosted lopinavir plus NRTIs with an
21 alternative NRTI-sparing regimen of ritonavir-boosted lopinavir plus raltegravir. Data from SELECT and
22 from two other large clinical trials (EARNEST⁷ and SECOND-LINE⁸) suggest that even in cohorts with
23 extensive NRTI resistance, second-line therapy with NRTIs remains effective. SELECT was held at 15
24 sites in low-income and middle-income countries. Patients with confirmed virological failure were
25 randomly assigned to receive ritonavir-boosted lopinavir plus NRTIs (n=255) or ritonavir-boosted
26 lopinavir plus raltegravir (n=260). In both groups, the prevalence of patients with NRTI mutations was

27 high. Resistance testing results were not available to caregivers and did not inform the selection of
28 NRTIs used in second-line therapy. By 48 weeks, the cumulative probability of virological failure was
29 12.4% (95% CI 8.3–16.5) in the NRTI group and 10.3% (95% CI 6.5–14.0) in the raltegravir group,
30 indicating that ritonavir-boosted lopinavir plus raltegravir was noninferior to, but not superior to,
31 standard of care (NRTIs).

32 Adverse events and serious adverse events were slightly less frequent in the raltegravir group than in
33 the NRTI group.⁶ EARNEST and SECOND-LINE reported that both regimens were comparably effective.
34 SECOND-LINE reported slightly more adverse events in the NRTI group than in the raltegravir group,
35 but EARNEST found no evidence that using NRTI in second-line therapy increased toxicity during 2
36 years of second-line therapy.^{7,8} SELECT, EARNEST, and SECOND-LINE all showed that ritonavir-boosted
37 lopinavir plus raltegravir is no less effective than the standard treatment. There is no doubt that
38 ritonavir-boosted lopinavir plus raltegravir is another second-line treatment option. But is there an
39 advantage to replacing NRTIs with raltegravir in second-line treatment in resource-constrained
40 settings? The finding that ritonavir-boosted lopinavir monotherapy was less effective than
41 ritonavir-boosted lopinavir plus NRTI suggests that NRTIs were still virologically active in second-line
42 therapy;⁷ the effectiveness and safety of ritonavir-boosted lopinavir plus raltegravir, and of standard
43 of care are largely comparable for the first 2 years of second-line treatment. However, NRTI-free
44 regimens might be better tolerated in the long term than standard second-line regimens because
45 NRTIs cause a wide range of long-term toxic effects.⁹ Although raltegravir is generally very well
46 tolerated, little is known about the long-term toxic effects of integrase inhibitors. Both second-line
47 options have the same dosing schedule.

48 Ritonavir-boosted lopinavir plus raltegravir has certain programmatic advantages over ritonavir-
49 boosted lopinavir plus NRTIs. Switching patients from a standard first-line regimen to ritonavir-
50 boosted lopinavir plus raltegravir can be done without resistance testing or considering within-class
51 resistance because two new drug classes are used in second-line therapy. But resistance testing is rare
52 in resource-limited settings and algorithms for selecting NRTIs without need for testing are feasible.

53 The main disadvantage of raltegravir is its limited availability and high cost. The current price of about
54 US\$600 per person-year for ritonavir-boosted lopinavir plus raltegravir¹⁰ makes this second-line
55 regimen around three times more expensive than the standard second-line regimen, and places a
56 heavy burden on the international organisations that supply these therapies to low-income and
57 middle-income countries. A recent modelling study estimated that the number of people on second-
58 line therapy will increase substantially and by 2020, between 0.5 million and 3 million people in sub-
59 Saharan Africa will need second-line ART depending on the scale-up of ART and monitoring strategy.¹¹
60 In the future, second-line drugs will make up more and more of the cost of HIV programmes,¹¹ and
61 alternative and cheaper second-line therapies should be explored. Until the price comes down,
62 expensive integrase inhibitors might be more beneficial as third-line therapies.

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64 Authors declare no competing interests.

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