# The best place for doravirine

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In *The Lancet HIV*, Chloe Orkin and colleagues[1] describe the results of the pooled analysis of two randomised studies, DRIVE-FORWARD and DRIVE-AHEAD, in which doravirine plus two nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) or in fixed-dose combination with tenofovir disoproxil fumarate and lamivudine maintained virological efficacy to 192 weeks.[1] This post-hoc analysis offers longer follow-up and a larger sample size compared with the individual base trials. Moreover, it provides new data for people who switched to doravirine after being on the comparator regimen for 96 weeks.

How can these data help when tailoring antiretrovirals for a person living with HIV who starts or switches therapy? Who might benefit the most from doravirine? The drug combinations used for the comparator groups of these two studies are no longer recommended first-line regimens for people with HIV who are antiretroviral therapy (ART) naive; however, darunavir is still largely used for its high genetic barrier to resistance mutations and efavirenz for the management of weight gain.[2] A head-to-head comparison between doravirine and second-generation integrase strand transfer inhibitors (INSTIs) will soon be reported in randomised clinical trials (NCT05924438 and NCT04636437). Moreover, real-world data are rapidly accumulating showing the high versatility of doravirine with any drug class in the ART backbone.

The pooled analysis by Orkin and colleagues[1] shows that doravirine-containing regimens were effective in the long term. A few patients developed genotypic resistance, suggesting that even if the genetic barrier of doravirine is higher than for other non-nucleoside reverse transcriptase inhibitors (NNRTIs), it is lower than that of the second-generation INSTIs used in either dual or triple regimens.[3] The findings also show that drug discontinuation was low and presents only in the initial treatment period, suggesting that doravirine has good long-term tolerability, similar to other NNRTIs. Doravirine also had an excellent metabolic profile, particularly regarding lipids and weight gain data. Is this enough to suggest doravirine as a champion for

| | Lipids | | | | Bodyweight | eGFR | Estimation of cardiovascular risk | Bone turnover | Comorbidities |
|---|---|---|---|---|---|---|---|---|---|
| | Total cholesterol | HDL | LDL | Triglycerides | | | | | |
| **RCT with ART-naive participants** | | | | | | | | | |
| DRIVE-AHEAD* (96 weeks) | Decreased | Decreased | Decreased | Decreased | No change | Decreased | Not applicable | Not applicable | Not applicable |
| DRIVE-FORWARD† (96 weeks) | Decreased | No change | Decreased | Decreased | No change | No change | Not applicable | Not applicable | Not applicable |
| Pooled analysis‡ (192 weeks) | No change | No change | No change | No change | No change | No change | Decreased | Not applicable | Not applicable |
| **RCT with ART-experienced participants** | | | | | | | | | |
| DRIVE-AHEAD§ (192 weeks, pooled) | No change | Decreased | Decreased | No change | No change | No change | Not applicable | Not applicable | Not applicable |
| DRIVE-FORWARD¶ (192 weeks, pooled) | No change | No change | Decreased | Decreased | No change | No change | Not applicable | Not applicable | Not applicable |
| DRIVE-SHIFT‖ (144 weeks) | Decreased | No change | Decreased | Decreased | No change | No change | Decreased | Not applicable | Not applicable |
| **Observational data** | | | | | | | | | |
| Real world evidence | Decreased | Decreased | Decreased | Decreased | No change | No change | Decreased | Not applicable | Decreased insulin resistance |

ART=antiretroviral therapy. eGFR=estimated glomerular filtration rate. NRTI=nucleoside (or nucleotide) reverse transcriptase inhibitor. RCT=randomised controlled trial. *Doravirine, lamivudine, and tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate at 96 weeks. †Doravirine plus two NRTIs versus ritonavir-boosted darunavir plus two NRTIs at 96 weeks. ‡Pooled analysis of DRIVE-AHEAD and DRIVE-FORWARD at 192 weeks. §Data on doravirine, lamivudine, and tenofovir disoproxil fumarate at 192 weeks in people with HIV who switched from efavirenz, emtricitabine, and tenofovir disoproxil fumarate at week 96 in DRIVE-AHEAD. ¶Data on doravirine plus two NRTIs at 192 weeks in people with HIV who switched from ritonavir-boosted darunavir plus two NRTIs at week 96 in DRIVE-FORWARD. ‖Doravirine, lamivudine, and tenofovir disoproxil fumarate versus current ART at 144 weeks.

***Table:*** **Available data on the effect of doravirine-containing regimens on metabolic outcomes**

metabolic health? Yes and no. The metabolic data described in registrational and real-world studies of doravirine both in ART-naive and ART-experienced people with HIV are summarised in the table.[4-6]

Metabolic health refers to a clinical construct that considers the net advantage for the patient regarding multiple metabolic parameters captured by body composition data (including BMI and visceral and liver fat accumulation), lipid fractions, glucose and insulin resistance, kidney function, and bone turnover. Moreover, metabolic health is not just the absence of metabolic diseases but rather a road map for heathy living. The pathway to improve metabolic health includes lifestyle interventions and a proactive antiretroviral approach to be considered in a patient-centred intervention.

Available metabolic data might suggest that doravirine can be used in both reactive and proactive strategies. Reactive strategies consider doravirine as a valuable option in people with HIV who have rapid weight gain when starting or switching an INSTI, or with obesity, or in people with dyslipidaemia. Proactive strategies consider doravirine in approaches for people at risk for metabolic diseases.

The metabolic health benefit of doravirine largely depends on the metabolic toxicities of the other drugs in the regimen, usually tenofovir disoproxil fumarate or tenofovir alafenamide, an INSTI, or a ritonavir-boosted protease inhibitor. In Orkin and colleagues' pooled analysis, the backbone included the NRTIs tenofovir disoproxil fumarate and tenofovir alafenamide. The current data suggest that doravirine coupled with tenofovir disoproxil fumarate reduces the effect of tenofovir disoproxil fumarate on estimated glomerular filtration rate over time, presumably by a neutral pharmacokinetic interaction with an NNRTI, which is very different to what happens when tenofovir disoproxil fumarate is associated with booster regimens.[7] A cautious attitude is still needed when prescribing tenofovir disoproxil fumarate to people with risk factors for osteoporosis (in particular in women in the menopause transition period) if dual-energy x-ray absorptiometry data are not available or in people with HIV with a progressive decline in glomerular filtration rate.

A limit of Orkin and colleagues' study is the absence of data on patient-reported outcomes, particularly quality of life. The DRIVE-AHEAD trial only reported neurocognitive adverse events for doravirine compared with the efavirenz-based regimen.[8]

In summary, these data contribute to understanding the position of doravarine in clinical practice and the tailoring ART regimens in long-term follow-up. The data suggest that doravirine is a valuable option for ART, with a particular benefit for the metabolic health of people with HIV.

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*Cristina Mussini, Giovanni Guaraldi
**cristina.mussini@unimore.it**

Department of Surgical, Medical, Dental, and Morphological Sciences (CM, GG) and Modena HIV Metabolic Clinic (GG), University of Modena and Reggio Emilia, Modena 41124, Italy; Department of Infectious Diseases, Azienda Ospedaliero-Universitaria, Policlinico of Modena, Modena, Italy (CM, GG)

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