Quad's in it for antiretroviral therapy?

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In *The Lancet*, the GS-US-236-0102[1] and GS-236-0103[2] study teams assessed the efficacy and safety of the latest single-tablet regimen—combining elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF)—against HIV-1 infection. Antiretroviral therapy has undergone substantial development. In addition to efficacy, tolerability, including the short-term and long-term side-effects combined with the convenience of a regimen, is a very important index to guide therapeutic choices. 26 antiretroviral drugs from six different classes are now approved, which has enabled individualised treatment in many patients. Furthermore, tremendous progress has been made in downscaling the pill burden of combination regimens, thus improving adherence,[3] a cornerstone in the treatment of HIV/AIDS. Treatment can often be given once daily with a single-tablet regimen as the simplest option. Therefore, new drugs should have at least equal efficacy (assessed in non-inferiority trials) and preferably an advantage over established regimens in their tolerability profile.

Treatment guidelines from the US Department of Health and Human Services recommend that antiretroviral therapy in treatment-naive adults with HIV should be the non-nucleoside reverse transcriptase inhibitor efavirenz (EFV), the ritonavir-boosted protease inhibitor atazanavir (ATV) or darunavir, or the integrase strand-transfer inhibitor raltegravir plus two nucleoside/nucleotide reverse transcriptase inhibitors—eg, emtricitabine and tenofovir disoproxil fumarate.[4] Of these preferred regimens, only efavirenz, emtricitabine, and tenofovir disoproxil fumarate are co-formulated in a single-tablet regimen. The investigators of GS-236-US-0102 and GS-236-0103 report two randomised, double-blind, phase 3, non-inferiority trials comparing EVG/COBI/FTC/TDF (also known as Quad) with two recommended first-line regimens in treatment-naive adults with HIV-1 infection.

Although Quad combines four molecules, it is composed of three antiretroviral drugs (elvitegravir, emtricitabine, and tenofovir disoproxil fumarate) plus a booster molecule (cobicistat). Elvitegravir is an investigational drug and the second member of the class of integrase strand-transfer inhibitors after raltegravir. In a trial of treatment-experienced patients, elvitegravir and raltegravir had similar efficacy combined with a ritonavir-boosted protease inhibitor and one other drug.[5] Elvitegravir is metabolised mainly via CYP3A4-5, which enables pharmacokinetic boosting and once-daily dosing.[6] By contrast, raltegravir once-daily is less effective than twice-daily dosing.[7] In Quad, elvitegravir is boosted by cobicistat, an investigational drug and derivate of ritonavir that has no antiviral activity, but is a more specific CYP3A inhibitor than ritonavir.[8]

GS-US-236-0102 treated 700 patients with EVG/COBI/FTC/TDF (n=348) or co-formulated EFV/FTC/TDF (n=352),[1] whereas GS-236-0103 treated 708 patients with EVG/COBI/FTC/TDF (n=353) or a once-daily ritonavir-boosted (RTV) protease inhibitor regimen of ATV/RTV+FTC/TDF (n=355).[2] EVG/COBI/FTC/TDF was non-inferior to both EFV/FTC/TDF (305 [88%] *vs* 296 [84%] patients had HIV RNA concentrations of less than the limit of detection [50 copies per mL] at week 48; difference 3·6%, 95% CI −1·6% to 8·8%) and ATV/RTV+FTC/TDF (316 [90%] *vs* 308 patients [87%]; difference 3·0%, 95% CI −1·9% to 7·8%) by a non-inferiority margin of 12%. Additionally, in patients with a high baseline viral load (>100 000 copies per mL, 34% of participants in GS-US-236-0102 and 41% in GS-236-0103) responses were similar (84% or 85% for EVG/COBI/FTC/TDF *vs* 82% for EFV/FTC/TDF or ATV/RTV+FTC/TDF).

Nausea was more common in patients given EVG/COBI/FTC/TDF than in those given EFV/FTC/TDF (72 [21%] *vs* 48 [14%] patients) whereas more patients in the EFV/FTC/TDF group had rash or CNS side-effects

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which are typically associated with efavirenz. Likewise, ocular icterus, a well-known potential side-effect of atazanavir, was less frequent in the EVG/COBI/FTC/TDF group than in the ATV/RTV+FTC/TDF group (two [1%] *vs* 51 [14%]). Although EVG/COBI/FTC/TDF resulted in fewer lipid perturbations (total, LDL, and HDL cholesterol were reduced) than did EFV/FTC/TDF, triglycerides and the ratio of total to HDL cholesterol were similar in both groups. Besides a decrease in triglycerides with EVG/COBI/FTC/TDF, lipid perturbations were similar to those noted with ATV/RTV+FTC/TDF. Numbers of adverse events leading to drug discontinuation were similar between the EVG/COBI/FTC/TDF and EFV/FTC/TDF (13/348 *vs* 18/352) or ATV/RTV+FTC/TDF (13/353 *vs* 18/355) groups. In the EFV/FTC/TDF group these events were mainly due to the expected CNS side-effects (6/18) and rash (5/18), whereas in the ATV/RTV+FTC/TDF group they were mainly due to gastrointestinal complaints (5/18) or ocular icterus (4/18). Discontinuations from Quad were mainly due to renal disturbances (6/26) when combining data for both studies.

Tenofovir, which was in all three regimens, is partly secreted in the proximal tubules where it can cause mitochondrial toxic effects that result in proximal tubulopathy.[9] Although findings from initial randomised controlled trials suggested that tenofovir might be safe,[10] case reports and observational studies have shown it to be potentially nephrotoxic.[11,12] What about a combination with a cobicistat-boosted regimen based on the integrase strand-transfer inhibitor class? Four patients in the combined Quad groups developed proximal tubular dysfunction leading to drug discontinuation, compared with none in the EFV/FTC/TDF or ATV/RTV+FTC/TDF groups.[13] Therefore, the independent data monitoring committee endorsed the decision to continue the blinded phase of the study from 48 to 192 weeks to clarify this issue. Use of Quad should be limited to patients with a normal renal function (estimated glomerular filtration rate cut-off for inclusion was >70 mL/min) until results in patients with mild to moderate renal function impairment are known (ClinicalTrials.gov, number NCT01363011).

Median concentrations of serum creatinine increased more in both EVG/COBI/FTC/TDF groups (13 μmol/L, IQR 5–20 in study GS-US-236-0102, and 11 μmol/L, 5–18 in study GS-236-0103) compared with EFV/TDF/FTC (1 μmol/L, –6 to 8) or ATV/RTV+FTC/TDF group (7 μmol/L, 1–15). This effect was attributed to cobicistat, reported in in-vitro studies to inhibit tubular secretion of creatinine[14] and thereby affecting estimated glomerular filtration rate (eg, on the basis of the Cockcroft-Gault equation) but not the actual rate.[15] The effect of cobicistat on intracellular concentration of tenofovir in the proximal tubular cells would likewise be informative. After approval, clinicians will nevertheless have to distinguish true renal toxic effects from pharmacologically induced increased serum creatinine.

What about virological failure? Overall virological failure was low in all groups (4% and 3% with Quad; 5% with EFV/FTC/TDF, and 2% with ATV/RTV+FTC/TDF). Of the patients for whom Quad was ineffective, 57% and 41% developed resistance mutations compared with 47% or none of those who failed EFV/FTC/TDF or ATV/RTV+FTC/TDF, respectively. In the Quad group, seven of eight and four of five patients had primary integrase strand-transfer inhibitor mutations (mainly Glu92Gln, but additionally Thr66Ile, Gln148Arg, and Asn155His, mostly resulting in cross resistance to raltegravir). Of note, nucleoside/nucleotide reverse transcriptase inhibitor mutations (Met184Val/Ile with or without Lys65Arg) were noted in all patients with Quad resistance, compared with two of eight patients given EFV/FTC/TDF or none of eight given ATV/RTV+FTC/TDF.

In conclusion, the accompanying two phase 3 studies[1,2] show that Quad has high efficacy and a good tolerability profile, with the limitations of potential drug interactions and a need to be taken with food. The under-representation of women in these studies, and absence of long-term safety data (especially for renal toxic effects) and resistance data, warrant further research. However, Quad will incite industry to generate further single-tablet regimens, ideally with other components, including those produced by different companies, enabling flexible treatment choices without tempering convenience for individual patients. In May, 2012, the US Food and Drug Administration advisory committee announced support for the approval of Quad to treat treatment-naive adults with HIV-1 infection. A final decision is expected by August, 2012.

*Rik Schrijvers, *Zeger Debyser*
Division of Molecular Medicine, Katholieke Universiteit Leuven, 3000 Leuven, Flanders, Belgium
zeger.debyser@med.kuleuven.be

We declare that we have no conflicts of interest.

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Protecting infants of HIV-positive mothers in Malawi

Child health in southern Africa is seriously threatened by the HIV epidemic: 20–30% of pregnant women are infected in most countries in this region. Prominent among threats to child health are HIV transmission and orphanhood. The avoidance or reduced duration of breastfeeding that can occur when women learn that they are HIV-positive is no less troubling than is the epidemic. New results from the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study done in Lilongwe, Malawi, reported by Denise Jamieson and colleagues in *The Lancet*,[1] remind us that limitation of breastfeeding duration is not suitable for HIV-infected women and their infants.

The BAN investigators previously reported that, in a trial comprising 2369 breastfeeding mothers infected with HIV-1, two antiretroviral interventions used during breastfeeding reduced HIV-1 transmission by 28 weeks.[2] The interventions were either daily nevirapine prophylaxis given to the infant or a triple antiretroviral drug regimen for the mother. Both interventions were continued to 28 weeks and then stopped. Women who met criteria for antiretroviral therapy recommended at the time for their own health (CD4 count <250 cells per μL) were not eligible for inclusion. These results contributed to the evidence base for WHO guidelines that now recommend either of the two interventions as prophylaxis when HIV-infected women do not meet the updated criteria for antiretroviral treatment (CD4 count >350 cells per μL).[3]

The new report[1] describes events after 28 weeks. Women were advised to stop breastfeeding between 24 and 28 weeks, much earlier than the Malawian norm of 24 months recommended for the general population.[4] However, at 32 weeks post partum 96% of women in the intervention groups and 88% in the control group reported no breastfeeding since their last visit at 28 weeks. Consistent with well established associations in infants born to HIV-negative mothers,[5] the sobering follow-up data show that mothers' compliance with early weaning resulted in significant increases in infant morbidity, growth faltering, and death.[1]

Comparison of age-specific morbidity and mortality before and after 28 weeks is not an optimum study design. Nevertheless, the finding that mortality after 28 weeks was significantly higher than before this point

Frederic Courbet/Panos

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