HIV RNA suppression rates after 24 weeks of treatment with etravirine, darunavir/ritonavir and raltegravir in the etravirine early access programme

Sirs: The next-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (formerly known as TMC125) has shown efficacy in the DUET trials in combination with a background regimen of darunavir with low-dose ritonavir (DRV/r), nucleoside analogue reverse transcriptase inhibitors (NRTIs) and optional enfuvirtide (ENF).[1,2] In the DUET trials, the percentage of patients with HIV RNA suppression <50 copies/mL was highest for patients who harboured virus sensitive to etravirine, and who combined etravirine with other active drugs in the background regimen.[3] Similar trends have been found in the BENCHMRK trials with the integrase inhibitor raltegravir,[4] and in the MOTIVATE trials with the CCR5 antagonist maraviroc.[5] Clinical pharmacology studies support the use of etravirine in combination with DRV/r,[6] raltegravir[7] or maraviroc.[8] Recent studies have evaluated the efficacy and safety of etravirine in combination with several combinations of these drugs:[9–12] these studies have shown high rates of efficacy after 24 weeks of follow-up.

The TMC125-C214 trial (etravirine early access programme) included patients with triple-class experience (NRTI, protease inhibitor [PI] and NNRTI) and who were unable to use currently approved NNRTIs owing to either intolerance or drug resistance. In Europe, patients were recruited from 10 countries. The patients received etravirine 200 mg twice daily with a range of background antiretrovirals (ARVs), which were selected based on treatment history and drug resistance. Of 941 patients with data available, 21% were women and 87% were Caucasian, with a mean age of 46 years. The baseline mean CD4 cell count was 299 cells/μL (range 0–1,647) and the baseline mean was HIV RNA 3.7 $\log_{10}$ copies/mL (range 1.6–6.5).

There were 176/941 patients with baseline HIV RNA levels above 400 copies/mL who started the combination of etravirine 200 mg twice daily, DRV/r 600/100 mg twice daily and raltegravir 400 mg twice daily. This was the most widely used combination of novel drugs and these patients were included in a preplanned analysis. The mean age of the patients was 46 years, with 82% men and 87% Caucasians. The baseline HIV RNA level was 4.3 $\log_{10}$ copies/mL (range 2.6–6.2 $\log_{10}$ copies/mL). The baseline CD4 count was 249 cells/μL (range 1–910 cells/μL). Of the 176 patients, 106 (60%) also used NRTIs: the most common were tenofovir (69 patients), lamivudine or emtricitabine (96 patients), zidovudine (9 patients) and abacavir (18 patients). Seventy patients (40%) used no NRTIs in their background regimen.

Follow-up data were available for 86 of the 176 patients at week 24. Figure 1 shows the percentage of evaluable patients with observed HIV RNA suppression below 400 or 50 copies/mL over 24 weeks of follow-up. Figure 2 shows the observed change in CD4 count during this time. By week 24, 74/86 (93%) evaluable patients showed HIV RNA suppression below 400 copies/mL, with a mean rise in CD4 count of 108 cells/μL. Patients using NRTIs in their background regimen showed a similar observed rate of HIV RNA suppression below 400 copies/mL (91%) versus those who did not use

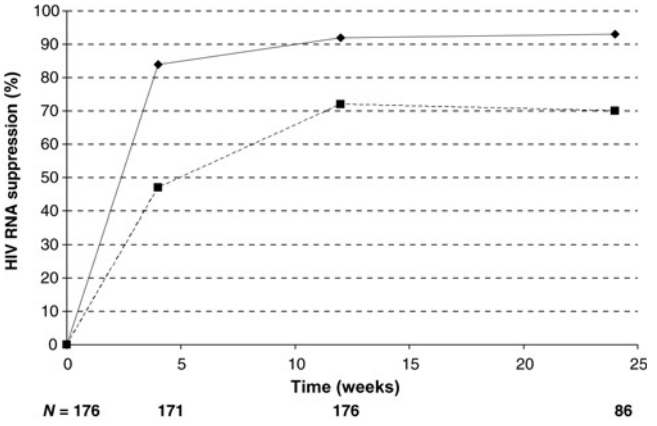

Figure 1 **HIV RNA suppression over time for patients taking etravirine, darunavir/ritonavir and raltegravir in the early access programme. Solid line: HIV RNA <400 copies/mL; dashed line: HIV RNA <50 copies/mL**

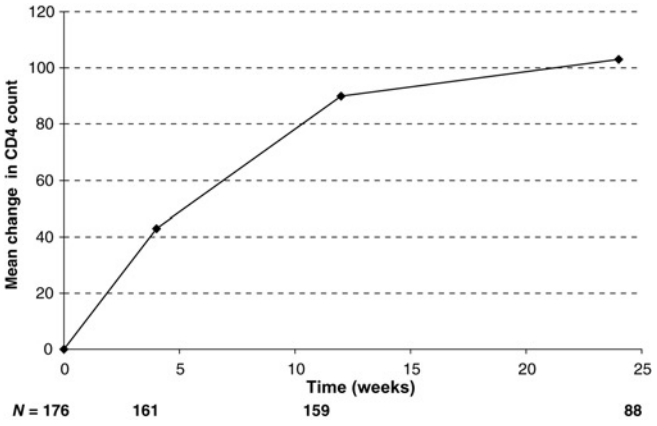

Figure 2 **Mean change in CD4 count over time for patients taking etravirine, darunavir/ritonavir and raltegravir in the early access programme**

NRTIs (97%). There were seven serious adverse events recorded among the 176 patients. Of these seven events, there were four cases of infection (pneumonia, campylobacter diarrhoea, upper respiratory tract infection and anal abscess), one myocardial infarction, one gastrointestinal disorder (Mallory–Weiss syndrome) and one case of lactic acidosis. None of these seven events was considered to be drug related by the investigators.

There are several limitations to this cohort study. First, the results are based on an observed data analysis – data collection is not as systematic in early access programmes, compared with prospective clinical trials, and follow-up time varies between patients. Second, patients were not randomized to receive or not receive NRTIs in their background regimen, and this comparison might be confounded by unknown biases. Thirdly, the HIV RNA testing was conducted locally at each investigational site, and different assays were used, with lower cut-off levels ranging from 48 to 75 copies/mL. Therefore, the results from the 50 copy analysis may underestimate the treatment effect.

In conclusion, the combination of etravirine, darunavir/ritonavir and raltegravir, associated or not with NRTIs, works

well in this unselected group of three class experienced HIV-positive patients with failure and/or drug intolerance. The virological and immunological response at six months is strong and the occurrence of serious adverse events is low and mostly not associated with the ARV treatment. These drugs are an attractive alternative to previously used multiple combinations of NRTIs, dual boosted PIs and ENF. It is not known whether nucleoside analogues contributed to the efficacy of novel combinations such as etravirine, darunavir/ritonavir and raltegravir. Randomized trials are needed to compare the efficacy of novel drug combinations with or without nucleoside analogues.

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Gonococcal inflammation of paraurethral glands around the external urethral orifice in males: a commonly encountered disease?

Sirs: Paraurethral glands can be found in both sexes, and have been mistaken as a structure present only in females for a long time. There is limited literature on the gonococcal inflammation of paraurethral glands around the external urethral orifice in males.[1,2] To further understand the clinical manifestation and treatment of this entity, we retrospectively analysed 82 cases of gonococcal inflammation of paraurethral glands around the external urethral orifice.

A total of 82 male patients with gonococcal inflammation of the paraurethral glands around the external urethral orifice were included in this study. All patients had engaged in extramarital sexual behaviour. The lesions began as an erythematous swelling of the external orifice of the urethra with tenderness and spontaneous pain. Following this an abscess presented several days later and perforated outward to form pinhead-like ostia. Pressure could cause expression of purulent or haemopurulent excretion from the ostium (Figure 1). Of all the patients, 78 had a solitary lesion and four had bilateral lesions. Dysuria, frequent micturition and purulent urethral discharge were all observed in 68 patients. Fourteen patients suffered from gonococcal urethritis, that had resolved. No lymphadenopathy or fever was observed. Laboratory examination revealed that culture for *Neisseria gonorrhoeae* was positive from exudates from the ostia of all 82 patients as well as from purulent urethral discharge from 68 patients, but neither exudates nor purulent discharge tested positive for *Chlamydia trachomatis*, *Treponema pallidum* or human immunodeficiency virus.

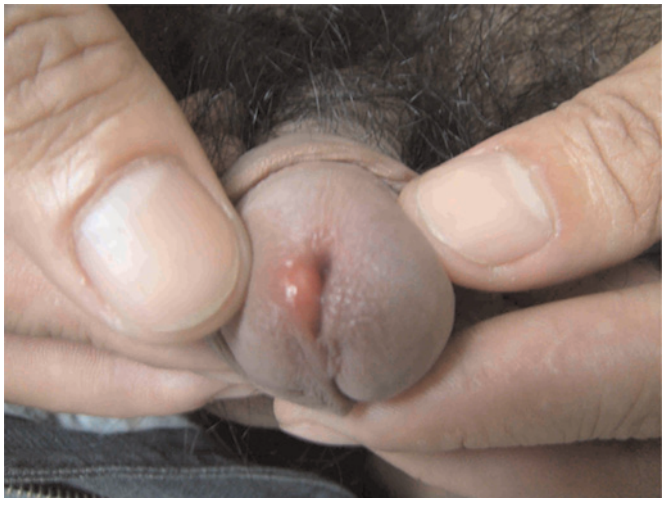

Figure 1 **Lesions of the paraurethral glands around the external urethral orifice**