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The EARNEST trial: new evidence regarding efficacy of second line ART regimens

The EARNEST trial was recently published in the New England Journal of Medicine.[1] This was an open-label randomised controlled trial conducted in multiple countries in sub-Saharan Africa that evaluated different second-line ART strategies for patients who had failed first-line ART in programmatic settings. In sub-Saharan Africa, because access to viral load monitoring is limited patients generally have substantial NRTI resistance at the time of switching to second line. This was true of participants in the EARNEST trial: intermediate or high level resistance to tenofovir was present in 57%, to zidovudine in 74% and to lamivudine in 95%. The resistance test was not used to make decisions regarding second line in this trial. Participants (n=1277 adults) were randomised to 1 of the 3 second line treatment strategies: Arm 1: lopinavir/ritonavir plus clinician-selected NRTIs; Arm 2: lopinavir/ritonavir plus raltegravir; or Arm 3: lopinavir/ritonavir monotherapy after an initial 12 weeks induction with lopinavir/ritonavir plus raltegravir. It was hypothesised that because patients in these settings have extensive NRTI resistance when starting second line that Arm 2 would be superior in terms of virologically suppression because it included 2 completely new ART classes, and that the monotherapy arm (Arm 3) would be virologically non-inferior to Arm 1 with reduced toxicity.

However, the findings were contrary to the hypotheses. At week 96, Arm 1 and 2 were equivalent in terms of participants suppressing to a viral load < 400 copies/ml (86% in both arms), but the monotherapy arm (Arm 3) was inferior (61%, $p < 0.001$). More patients in the monotherapy arm developed intermediate to high level lopinavir resistance (18% versus 2% and 1% in Arm 1 and 2 respectively). There was no significant difference in adverse events related to study drugs between arms.

These findings have important implications. The findings suggest that even when there is significant resistance to NRTIs after first-line failure they still make an important contribution to achieving high levels of viral load suppression in second line (86% suppression < 400 copies/ml, and superiority of Arm 1 over lopinavir/ritonavir monotherapy) and that introducing a new class (raltegravir - an integrase inhibitor) in addition to a PI is not necessary in second line. The lopinavir/ritonavir plus raltegravir regimen is a second line option in patients who cannot tolerate NRTIs – it is however not superior to AfA's currently recommended second line regimen of a PI plus 2 NRTIs. We generally recommend saving the integrase inhibitor class for third line. In the EARNEST trial the activity of the NRTIs that was demonstrated in second line despite resistance in many patients is likely due to a combination of residual antiviral activity plus their "crippling" effect in maintaining a less fit mutant virus in circulation.

Reference

1. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. **Paton** NI, et al N Engl J Med. 2014;371(3):234-47.

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Rilpivirine (Edurant®) has recently been registered in South Africa and is competitively priced. Rilpivirine is a second generation non-nucleoside reverse transcriptase inhibitor (NNRTI). Like etravirine, it retains activity with some resistance mutations that compromise the first generation NNRTIs efavirenz and nevirapine.[1] Rilpivirine has a long half life of 34-55 hours and is given once daily with a meal.[1] Rilpivirine requires low stomach pH for adequate absorption, so it should not be co-administered with proton pump inhibitors. Antacids or H_2 blockers should be administered 12 hours before or 4 hours after administration of rilpivirine.[2] Rilpivirine is metabolised by the cytochrome P450 enzyme CYP3A4. Unlike the other NNRTIs, rilpivirine does not induce or inhibit the metabolism of other drugs. Co-administration with strong CYP3A4 inducing drugs (e.g. rifampicin, phenytoin, carbamazepine) is contraindicated as this results in significant reductions in rilpivirine concentrations.[2] Co-administration with strong CYP3A4 inhibiting drugs (e.g. clarithromycin, cimetidine, ketoconazole) results in increases in rilpivirine concentrations, but the magnitude of the increase is modest and dose adjustment is not required.[2] High doses of rilpivirine prolong the QT interval, but not at the recommended dose of 25 mg daily. Even when rilpivirine is co-administered with drugs that inhibit CYP3A4, the resulting concentrations are not elevated to the extent that could result in QT prolongation.[2] The most common adverse drug reactions to rilpivirine are insomnia, depression, headache, and rash.

The efficacy and tolerability of rilpivirine was compared with efavirenz in ART-naïve participants in two randomised controlled trials, ECHO and THRIVE. In both trials there was no difference in virological suppression.[3] Rilpivirine was better tolerated than efavirenz with significantly lower risk of rash and neuropsychiatric adverse drug reactions.[3] Lipids did not significantly alter in the rilpivirine arms, while total cholesterol, LDL cholesterol and triglycerides increased in the efavirenz arms.[3] However, there were higher rates of virologic failure and a higher proportion of patients developed NNRTI resistant mutations in the rilpivirine arms in patients with a baseline viral load of >100,000 copies/mL.[4,5] In a combined analysis of the ECHO and THRIVE trials virologic failure occurred in 5% of participants in both arms with baseline viral loads ≤100,000 and 7% and 17% in the efavirenz and rilpivirine arms respectively in participants arms with baseline viral loads >100,000.[4] Therefore, in ART-naïve people, rilpivirine is only recommended if the baseline viral load is ≤100,000. The ability of rilpivirine to maintain virologic suppression in patients who achieved suppression on protease inhibitor regimens was explored in the SPIRIT trial.[6] At the 24 week endpoint the viral load was <50 copies/ml in 93.7% and 89.9% of the rilpivirine and protease inhibitor arms respectively. Rilpivirine can be used in salvage therapy together with a protease inhibitor depending on the pattern of NNRTI mutations.

References

1. Sharma M, Saravolatz LD. Rilpivirine: a new non-nucleoside reverse transcriptase inhibitor. J Antimicrob Chemother. 2013 Feb;68(2):250-6.
2. Crauwels H, van Heeswijk RP, Stevens M, Buelens A, Vanveggel S, Boven K, Hoetelmans R. Clinical perspective on drug-drug interactions with the non-nucleoside reverse transcriptase inhibitor rilpivirine. AIDS Rev. 2013 Apr-Jun;15(2):87-101.
3. Cohen CJ, Molina J, Cahn P, et al. Efficacy and Safety of Rilpivirine (TMC278) Versus Efavirenz at 48 Weeks in Treatment-Naive HIV-1–Infected Patients: Pooled Results From the Phase 3 Double-Blind Randomized ECHO and THRIVE Trials. J Acquir Immune Defic Syndr 2012;60:33–42.
4. Rimsky L, Vingerhoets J, Van Eygen V, et al. Genotypic and phenotypic characterization of HIV-1 isolates obtained from patients on rilpivirine therapy experiencing virologic failure in the phase 3 ECHO and THRIVE studies: 48-week analysis. J Acquir Immune Defic Syndr. 2012;59(1):39–46.
5. Porter DP, Kulkarni R, Fralich T, Miller MD, White KL. Characterization of HIV-1 drug resistance development through week 48 in antiretroviral naive subjects on rilpivirine/emtricitabine/ tenofovir DF or efavirenz/emtricitabine/tenofovir DF in the STaR study (GS-US-264-0110). J Acquir Immune Defic Syndr. 2014 Mar 1;65(3):318-26.
6. Palella F, Tebas P, Gazzard B et al. SPIRIT study: switching to emtricitabine/rilpivirine/tenofovir DF (FTC/RPV/TDF) single tablet regimen (STR) from a ritonavir-boosted protease inhibitor and two nucleoside reverse transcriptase inhibitors (NRTIs) maintains viral suppression and improves serum lipids. Abstract TUPE0080. 19th International AIDS Conference on HIV Pathogenesis, Treatment, and Prevention, Washington, DC, 2012.

The value of a psychological report in treatment failure

All too often, the question is asked "What antiretroviral regimen should I use for this patient starting 2nd line or salvage therapy?", when the really important question is "why did this patient fail 1st or 2nd line ART?" If we spent a little more time on the latter and less on the former, which is the easy part, the outcome for individual patients would be better, and the future of antiretroviral susceptibility for this, and the next generations, more likely to be prolonged.

HIV prescribers know that there are a multitude of reasons why patients fail to adhere to ART. Some are simple, some multifactorial, and others hidden. On the whole, we as doctors are lousy at adherence. One study of 66 HIV service providers showed that only just over half were able to recognize depression and one third recognized mental illness.[1] In addition, our HIV counsellors are often under-trained, over-worked, at the end of a phone rather than face-to-face, and not given the tools with which to deal with the complex personal, social and psychological problems that our patients present them with. Moreover, they are in the main, unable to recognize psychiatric disease, which is often also missed by HIV prescribers. Having worked in an HIV clinic with a psychiatrist who saw all patients failing ART and any other referrals from our team, a considerable number of patients with undiagnosed depression, anxiety disorder, personality disorder or other psychiatric illness impeding adherence, were picked up, not by the HIV physician or counselor, but by the said psychiatrist. A study from Uganda of 368 HIV-positive persons screened for major depressive disorder identified major depressive disorder in 17.9 % of the screened group, and in 2.1 % of the non-screened group [OR = 9.65, CI = (4.54-20.50)]. The screened individuals were 7.8 times more likely to receive antidepressants (95 % CI = 3.04-20.24).[2]

No patient in South Africa should be prescribed salvage therapy, nor arguably, 2nd line ART without a mandatory psychiatric evaluation by a trained practitioner, to ensure that mental illness is not being missed.

References

1. Mall S, Sorsdahl K, Struthers H, Joska JA. Mental health in primary Human Immunodeficiency Virus care in South Africa: A study of provider knowledge, attitudes and practice. Journal of Nervous & Mental Disease 2013;201(3):196-201.
2. Akena D, Stein DJ, Joska J. Does screening HIV-positive individuals in Uganda for major depressive disorder improve case detection rates and antidepressant prescription? AIDS Behav. 2013 Oct;17(8):2802-7. doi: 10.1007/s10461-012-0383-y.

Clinical Case Report - 35 year old male patient on a PMB Medical Scheme Option (Subject to State Protocols)

After registering on the Aid for AIDS programme, the patient was started on a first line antiretroviral regimen in Feb 2011. This was a fixed dosed combination product containing three antiretrovirals – Tenofovir, Emtricitabine and Efavirenz.

In Oct 2012, due to treatment failure and in consultation with our medical advisor, he was changed to a second line regimen of Tenofovir, Emtricitabine and Lopinavir/ritonavir. Although the preferable second line regimen would have been Zidovudine, Lamivudine and a protease inhibitor, the treating doctor requested to use Tenofovir, Emtricitabine and a protease inhibitor as there was a possibility that he may have had some exposure to zidovudine prior to starting Tenofovir, Emtricitabine and Efavirenz. We agreed with his request. Despite adherence counseling, the response to the second line combination was sub-optimal.

In Oct 2013, he was diagnosed with tuberculosis and commenced on a Rifampicin containing TB regimen and the dose of Lopinavir/ritonavir was gradually increased to four tablets twice a day in order to counteract the enzyme inducing effect of Rifampicin.

In Nov 2013, the viral load remained unsuppressed despite the patient claiming adherence to treatment. He was also clinically unwell and was admitted to hospital with septicaemia for almost a month. In view of his clinical status and poor response to treatment, an HIV resistance test was done in the hope of constructing an effective regimen which would suppress his viral load and increase his CD4 count and thus reduce the risk of developing opportunistic infections and progression to AIDS.

The resistance test results showed a bad resistance profile with multiple mutations and it was decided to discuss the case with two of our infectious disease consultants at our weekly clinical meeting. Their recommendation was to change treatment to a third line or salvage regimen of Tenofovir/Emtricitabine, Zidovudine, Raltegravir and boosted Darunavir. As Rifampicin cannot be used with Darunavir, we would have to change this to a Rifabutin containing TB regimen. All TB therapy would be funded from the HIV benefit as Rifabutin is not available at State TB clinics.

We also suggested that he see a psychologist first to ensure commitment to the salvage regimen as this was the last currently available regimen and it was clear that treatment adherence was still a problem. The recommendations were discussed with the treating doctor who agreed to implement them.

The patient was seen by a psychologist and a comprehensive report was received from her towards the end of 2013. In her report, it was noted that that the patient acknowledged that he was not fully adherent to his previous regimens but now realized the importance of taking his salvage treatment as this would most likely improve his health and increase his longevity. He accepted the fact that he would have to take lifelong therapy and was able to see this in a positive light. He was motivated to recover and committed to take his salvage regimen.

In view of this report, both salvage ART and TB treatment was approved by AfA. As these drugs are very expensive, the cost of the regimen for the year was going to exceed the available annual benefit that he had. A motivation was then sent by our medical advisor to the fund manager of the scheme requesting additional funding. This was immediately approved by the scheme.

It is important to note that within a month of starting the recommended regimen there was a significant improvement in his results. His HIV viral load had decreased by 99% and is now undetectable. The primary objective of antiretroviral therapy is viral load suppression. This is associated with immunological recovery and a reduced risk of opportunistic infections, as well as reduced mortality.

This case illustrates the value of HIV managed care. Various interventions were required in order to ensure commitment to taking effective treatment and the outcome clearly shows that they were beneficial. The new treatment combination has resulted in viral load suppression and has reduced the risk of opportunistic infections and disease progression, as well as allowed the TB to be effectively managed by avoiding significant drug interactions. Optimum adherence is essential to manage both HIV and TB and the recommendation to refer the patient for psychological assessment before commencing salvage therapy has clearly paid dividends.