

Healthcare Professional Newsletter

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Early ART initiation as a factor in combating antibiotic resistance

Increasing bacterial resistance to antibiotics is recognised as a major global health threat. Modelling suggests that by 2050, the current number of deaths as a result of bacterial resistance is set to rise from 700,000 per year to over 10 million deaths annually. Although tuberculosis is a major driver of the increase, it is resistance to other bacteria that are causing greatest concern. The identification of new transferable resistance genes that confer resistance to colistin, an antibiotic of last resort for the treatment of multi-drug resistant Gram-negative bacteria in humans, heralds the onset of a new era of medicine, where common bacterial infections are untreatable.

Prevention of infection is key to reducing bacterial resistance, as the main driver is misuse and overuse of antibiotics. The greatest impact will come from altering the social determinants of infection such as provision of clean water and sanitation, and from vaccination against bacterial and viral infections that drive antibiotic consumption. However, a recent publication from the INSIGHT START study group has confirmed previous findings that early initiation of ART can impact on the incidence of severe bacterial infection.

The START trial showed that early initiation of ART in patients with CD4 counts >500 cells/mm³ reduced the risk of AIDS and non-AIDS morbidity and mortality by 57% compared to those that deferred initiation until their CD4 count was <350 cells/mm³ or an AIDS-related event or pregnancy occurred.

Now, a further analysis of the data from this cohort has shown that early initiation also decreased the incidence of severe bacterial infections as defined by tuberculosis, bacterial pneumonia, or any infection that was a grade 4 event, required hospitalisation, or resulted in death. The reduction in severe bacterial infection compared to the delayed treatment arm was 61%, and in multivariate analysis, was associated with initial rise in CD4 count. Reduction in cases of tuberculosis only accounted for one fifth of the impact, indicating that ART is also important in preventing common bacterial infections.

The protective effect of early ART initiation in reducing the risk of a broad spectrum of severe bacterial infections is an important factor in low- and middle-income countries with a high infection burden from common bacterial infections. It constitutes a further piece of evidence to support the early initiation of ART in any patient ready to take treatment.

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Dolutegravir: not as monotherapy

As previously reported in our newsletter (June 2016), dolutegravir is a second generation integrase inhibitor that has a higher barrier to resistance than raltegravir. No integrase resistance-associated mutations have been reported in ART-naïve patients receiving dolutegravir as part of a three drug ART regimen in several clinical trials cumulatively including over 1000 participants receiving dolutegravir.

Given this high barrier to resistance, there has been interest as to whether dolutegravir may be effective in a two drug ART regimen or even as ART monotherapy.

Two studies reported at the recent Conference on Retroviruses and Opportunistic Infections (CROI) held in Seattle, US, 13-16 February 2017, strongly indicate that dolutegravir monotherapy should not be used as several patients developed integrase inhibitor resistance, including the selection of integrase resistance mutations not previously reported with dolutegravir use.

The first was a retrospective study including 178 patients from 3 cohorts in Europe and North America who were prescribed dolutegravir monotherapy. These were ART-experienced patients with no prior integrase inhibitor virological failure who were switched from different ART regimens to dolutegravir monotherapy. Eleven (6.1%) had virological failure and 7 (3.9%) selected integrase inhibitor mutations on dolutegravir monotherapy. All 7 of these patients had a viral load < 400 copies/ml when they switched to dolutegravir monotherapy. The mutations selected included 148R/H and 155H, that are seen with raltegravir failure. The median time to detection of first mutation was 6 months on dolutegravir.

A controlled trial in the Netherlands randomised patients with suppressed viral loads on combination ART to switch to dolutegravir monotherapy or continue ART. The trial was stopped early when 8 of 96 patients who switched to dolutegravir monotherapy developed virological failure, 3 of whom developed integrase resistance mutations. The investigators concluded: "The genetic barrier of dolutegravir monotherapy is insufficient to allow for maintenance monotherapy."

While selection of integrase resistance mutations was infrequent (<5% of patients) these studies involved relatively short term follow-up. The findings of these two studies indicate that the resistance barrier of dolutegravir is insufficient to allow for the drug's use as monotherapy and AfA strongly advises against such an approach.

Furthermore, these findings indirectly support our previous newsletter (August 2016) advice that dolutegravir should not be used in second line ART when it cannot be established that the patient's virus is still susceptible to at least one of the accompanying NRTIs in the regimen. In patients on second line ART it is quite possible that they may have resistance to one or both NRTIs in their regimen because of resistance selected at first line failure. In cases where there is resistance to both NRTIs in their regimen, combining these NRTIs with dolutegravir in a regimen may result in "effective dolutegravir monotherapy" with the risk of selecting integrase inhibitor resistance. Therefore, until there is further evidence regarding the virological efficacy and resistance barrier of dolutegravir in second line ART regimens, we advise against the use of dolutegravir in second line. There are special circumstances where dolutegravir may be considered in second line (e.g. multiple drug intolerance). These cases would need to be discussed with AfA.

References:

1. Blanco et al. Pathways of resistance in subjects failing dolutegravir monotherapy. CROI 2017, Abstract 42. <http://www.croiconference.org/sessions/pathways-resistance-subjects-failing-dolutegravir-monotherapy>
2. Wijting et al. Dolutegravir as maintenance monotherapy for HIV-1: a randomized clinical trial. CROI 2017, Abstract 451LB. <http://www.croiconference.org/sessions/dolutegravir-maintenance-monotherapy-hiv-1-randomized-clinical-trial>

BREATHER – Can HIV+ youth safely have a weekend off their antiretroviral medication?

HIV-related deaths have decreased for all age groups except adolescents since 2010. Adolescent death rate has actually increased.¹ Adolescence, is a time of transition from childhood to adulthood with unique psychosocial and physical changes. Peer influence and establishing sexual relationships are crucial components. HIV+ youth face additional challenges such as disclosure of HIV status and adherence to medication. Weekends are a time of intense social engagement, when taking medication may be especially challenging and inconvenient. What if a weekend medication holiday was feasible and safe? A 5 day on and 2 day off strategy had already been successfully studied in adults.² In contrast, a 3-day ARV-free period was unsuccessful.³

The BREATHER (**BR**Eaks in Adolescent and child **TH**erapy using **E**favirenz and two **nR**tis) trial, from the Paediatric European Network for Trials in AIDS (PENTA), supports medication-free weekends, as long as carefully applied and the youth are fully engaged.⁴ The study population comprised 199 young people (8 – 24 years of age; 21% above 18 years; 90% perinatally infected) in 11 countries from Europe, Asia, North America, South America and Africa. The only African site, Uganda, contributed 70 participants. Antiretroviral therapy comprised daily efavirenz (600mg) and 2 nucleoside reverse transcriptase inhibitors (mostly tenofovir and emtricitabine). Virological suppression for at least 12 months and a CD4 count above 350 cells/mm³ were entry criteria. Participants were randomised to short course therapy (SCT) or continuous therapy (CT). All participants had 12-weekly real-time plasma viral load monitoring. For a single HIV-RNA ≥ 50 copies/mm³, participants returned for confirmatory viral load testing (usually within 7 days) and returned to CT for a confirmed elevation.

The primary outcome was confirmed HIV-RNA ≥ 50 copies/ml by week 48; the acceptable non-inferiority margin was 12%. The actual difference for failure (SCT minus CT) was -1.2% (90% CI -7.3 to 4.9; p=0.75). Immunological, safety and resistance profiles were similar. Ninety percent of SCT participants reported that treatment breaks made socialising easier than daily ART. All described more treatment side-effects than they disclosed in clinic with SCT participants reporting relief from side-effects at weekends. There was no difference in toxicity and some cost saving in the SCT arm. Data from longer follow-up are awaited. This study represents one of the first focusing on adolescent issues and represents a potentially useful strategy in engaged and committed youth. However, it should be noted that the findings only apply to young people whose viral load has been suppressed for >12 months.

References

1. Fund UNCs. *For every child, end AIDS. 7th stocktaking report, 2016*. New York UNICEF HIV and AIDS Section United Nations Plaza, New York, NY 10017, USA;2016.
2. Cohen C, Colson A, Pierone G, et al. The FOTO study: The 48 week extension to assess durability of the strategy of taking efavirenz, tenofovir and emtricitabine Five days On, Two days Off (FOTO) each week in virologically suppressed patients IAS; 2009; Cape Town.
3. Rudy BJ, Sleasman J, Kapogiannis B, et al. Short-cycle therapy in adolescents after continuous therapy with established viral suppression: the impact on viral load suppression. *AIDS Res Hum Retroviruses*. 2009;25(6):555-561.
4. Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents, and young adults (BREATHER): a randomised, open-label, non-inferiority, phase 2/3 trial. *The Lancet HIV*. 2016;3(9):e421-e430.

Diagnosing “elite controllers”

Elite controllers are HIV-infected people with a sustained suppressed viral load in the absence of ART. Their viral loads may intermittently “blip” up to 1,000 copies/mL. Most, but not all, elite controllers have a normal CD4 count. Elite controllers are uncommon, occurring in 1 person in every 200-300.

It is essential that the HIV antibody tests were done by a laboratory rather than rapid antibody tests done on site, and that two ELISA tests are both positive from different manufacturers (this is standard practice in the laboratory). Antibody tests can very rarely be false positives, so under ideal circumstances additional confirmatory tests can be done. The best confirmatory test is the HIV Western blot assay, but not all laboratories have this assay. A qualitative PCR (typically used for diagnosing HIV infection in infants) is also confirmation of HIV infection, but it may be negative in elite controllers.

The viral load assays only detect HIV-1 infection. Currently used ELISAs cannot distinguish HIV-1 from HIV-2, and the western blot is also unreliable for diagnosing HIV-2. HIV-2 is extremely rare in South Africa, but if the patient or their partner is from West Africa then HIV-2 infection needs to be ruled out with an HIV-2 PCR assay.

The 2017 Annual Update Module for Afa’s CPD-accredited Internet-based HIV management modular training programme is now available!

Online modular training for doctors and other healthcare professionals in HIV medicine offers a practical solution to gain HIV management skills. It is particularly suitable for those working outside of the major centres. Individual modules or the full training programme may be completed. The course has been developed by Professor Gary Maartens, who is an acknowledged expert in HIV management and has participated in the development of HIV treatment guidelines both nationally and internationally. The modules cover the basics of HIV management and reflect current best practice, both nationally and internationally.

The annual HIV update module based on new guidelines and advances in HIV management is now available and, as with the other modules, is fully CPD-accredited.

The contents of the new update module include:

- Global picture of HIV epidemic
- Cheap rapid TB test saves lives in inpatients
- TB preventive therapy
- MTCT trial of ART
- HIV prevention results from vaginal ring dapivirine trials
- Long-acting intramuscular ART
- Doravirine: an investigational NNRTI
- ART for prevention - disappointing results from RCT
- New WHO consolidated guidelines

Registration on the course is free of charge and is open to all doctors as well as other interested healthcare providers.

Please go to <http://training.aidforaids.co.za/> to register, using your professional council registration number and follow the simple instructions. If you do not have a professional council number your ID number may be used.