Taking a BREATHER: Can young people on efavirenz-based ART regimens have two days off ART each week?

Challenges of HIV treatment for young people

Antiretroviral therapy (ART) has transformed HIV from a life-threatening disease to a chronic infection. Recent World Health Organisation guidelines recommend immediate ART for all people living with HIV, including children and young people. This means there will be a growing number of children and young people on life-long ART.

HIV treatment can be challenging. Treatment needs to balance maximising the benefit of ART while minimising the long-term side-effects. It is also important that people on ART maintain good adherence over the long-term, to prevent drug resistance developing, and maximise future drug options. These issues are particularly acute for young people, who face a lifetime of HIV treatment. The transition from childhood to adulthood is often associated with lower adherence. Daily ART can also interfere with young people’s social lives, with needing to take drugs at specific times often conflicting with a desire to keep their HIV status secret and socialise with others.

Short cycle therapy is a strategy that may help address some of these challenges.

It aims to maintain viral suppression during planned short breaks from ART, reducing ART intake, long-term toxicities and costs. Various versions of short cycle therapy have been tested, the most promising of which seems to be taking ART

Key points

- Taking antiretroviral therapy daily can be challenging, particularly for young people living with HIV: it’s a daily reminder of their HIV status; it can interfere with social activities; and some experience side-effects.

- Taking weekends off efavirenz-based ART was as good as taking ART every day for young people in terms of viral load suppression and immune status after 1 year.

- Moving to short-cycle therapy was difficult for young people at first, but once they got used to the new routine they preferred it: it gave them more freedom in their social lives, and was a break from drug-related side-effects. Some said that they made more effort taking their drugs well during the week.

- This approach is not suitable for everyone: for it to work it needs the virus to already be suppressed, good adherence to treatment during weekdays, and an ART regimen that includes an antiretroviral that stays active against the virus for a long time (efavirenz was used in BREATHER). Young people also had their virus levels in the blood monitored at least 4 monthly.

- Before this approach is rolled-out beyond the trial, we need evidence of its longer-term safety and efficacy.
daily for five days a week, and then having two days off treatment each week.

Short cycle therapy depends upon people being on an ART regimen that includes a drug that has long-lasting activity against the virus, such as efavirenz, which has a plasma half-life of 40-91 hours.

Two small randomised controlled trials have found this five days on, two days off strategy to be non-inferior to continuous (daily) therapy for adults. This strategy could potentially allow young people to take weekends off treatment, which may help to address some of the social and side-effect challenges of daily ART, but we need evidence that it is safe, effective and acceptable to young people. The BREATHER trial set out to test this.

Is it safe for young people on Efavirenz to take weekends off?

Viral suppression

BREATHER found no significant difference in the number of young people who had a viral load of more than 50 copies per ml at 48 weeks (six young people in the short cycle therapy arm versus seven in the continuous therapy arm). Those on the short cycle therapy arm who had a viral load of more than 50 copies per ml resumed daily ART, and five out of the six resuppressed, three without changing regimen. Only three of the seven participants in the continuous therapy arm with viral load of more than 50 copies resuppressed the virus. There was no evidence that short cycle therapy was inferior to continuous therapy in terms of viral suppression. BREATHER also found no significant differences between the arms in very low levels of viral suppression (less than 10-20 copies/ml), viral resistance, CD4% or CD4 cell count.

Side-effects

By week 48 there had been 13 reports of grade 3 or grade 4 adverse events in the short cycle therapy arm, and 14 in the continuous therapy arm. The most common adverse event was decreased neutrophil count (two participants on the short cycle therapy arm, versus 6 in the continuous therapy arm). Two ART-related adverse events were reported in the short cycle therapy arm versus 14 in the continuous therapy arm (lipodystrophy and gynaecomastia were the most common).

The BREATHER trial

The BREATHER trial is a Phase II, randomised controlled non-inferiority trial. It tested whether short cycle therapy (five days on ART, two days off) is as good as daily ART in terms of viral load suppression. It also looked at any effect on immune status, HIV mutations, side-effects, adherence and acceptability. There were 199 participants in BREATHER, aged from eight to 24 years, on regimens containing efavirenz plus two or three NRTIs. Participants had been on ART for at least a year (median 6.1 years on ART at baseline), had suppressed viral loads, and CD4 cell counts of >=350cells/µl at enrolment. The trial took place in Europe, Uganda, Thailand, Argentina and the USA. It opened in March 2011.

As part of the study in-depth qualitative interviews are being carried out with 40 participants, to gain insight into the acceptability of SCT, and the experience of participants in managing their treatment.
In the qualitative sub-study young people reported side-effects that they did not mention to their doctors. These included dizziness, lack of energy and not feeling themselves. Those on short cycle therapy sometimes reported that these side-effects reduced during their weekends off treatment.

**Inflammation**

BREATHER looked at 19 biomarkers of inflammation, vascular injury and disordered thrombogenesis. There were no differences in any of these markers, except D-dimer, which was lower in the short cycle therapy arm than the continuous therapy arm. This is unlikely to be of clinical significance, and may be due to chance.

**Changes in regimen**

By week 48, eight young people on the short cycle therapy arm had reverted to daily treatment: six because their viral load had become detectable, one because they had poor adherence, and one because they stopped efavirenz due to side-effects. Most of those going back to daily treatment had viral load return to undetectable levels.

**Adherence**

There was no significant difference in adherence to scheduled doses between the arms, with both groups of young people having good adherence to their dosing schedule. Young people in the short cycle therapy arm did seem to be taking their weekends off, while those in the daily treatment arm did seem to be taking ART at the weekend. As expected, young people on short cycle therapy had lower levels of drug in their blood than those on continuous therapy. In the qualitative interviews young people from both arms reported sometimes missing doses without telling their clinicians.

**What did young people think about short-cycle therapy?**

The young people in the qualitative sub-study reported that, prior to starting on short cycle therapy, they were worried that they may find it confusing. These concerns eased once they had got used to short cycle therapy. Many of them said that they found it difficult to adapt to short cycle therapy, taking around four to 10 weeks to establish new routines. But they did get into new routines eventually.

Short cycle therapy was valued by young people, who reported that it had a positive effect on their social lives. They said it allowed them to go out with friends more easily, and stay at friends houses for the first time. They could relax at weekends without worrying about having to take their ART, or being seen doing so.

Another perceived benefit of short cycle therapy was that it gave them a break from side-effects that they did not report to their doctor (dizziness, feeling spaced or high, problems with concentrating, not feeling quite themselves).

Despite the high acceptability of short cycle therapy, the young people in the qualitative sub-study did not think that it would work for everyone. They recognised that it required good adherence to the scheduled doses.

**What are the gaps in the evidence?**

While the BREATHER results look promising for short cycle therapy, the data so far are short-term. Before it can be implemented more widely, we need evidence of the longer-term safety of the approach. BREATHER has continued follow-up for another 2 years, to help address this question, and these results should be available in 2017.

Short cycle therapy reduces the amount of drug needed, but requires close monitoring and regular viral load testing. Where this is already done routinely, short cycle therapy may be cost-effective or cost-saving. But the cost impact is less clear where regular viral load monitoring is not already taking place. Despite the recent drive to increase use of viral load testing, there are still many settings where it is not routinely available. It is unclear if short cycle therapy is safe without this close, regular monitoring, particularly as young people rely on test results to decide whether to tell
clinicians about any missed doses. Further research is needed to answer this question.

All the young people in BREATHER were on regimens including efavirenz. More research is needed to see whether ART regimens using other long-acting drugs (eg. TAF and dolutegravir) are appropriate for a short cycle therapy approach. These alternative drugs may have advantages over efavirenz, such as a higher barrier to resistance.

Short cycle therapy is not the only potential approach being developed to help young people on ART. Depot injectable ART may be an alternative way of addressing the challenges young people living with HIV face, but it is currently early days for this approach.

Further information


Credits

This briefing paper was written by Annabelle South, Di Gibb, Sara Paparini and Karina Butler on behalf of the BREATHER (PENTA 16) Trial Group.

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