BREATHER (PENTA 16) short-cycle therapy (SCT) (5 days on/2 days off) in young people with chronic human immunodeficiency virus infection: an open, randomised, parallel-group Phase II/III trial

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Scientific summary

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Scientific summary

Background

As the cohort of children with human immunodeficiency virus (HIV) infection in the UK and Ireland ages (median age 5.1 years in 1996, increasing to 9.9 years in 2006 and 13.6 years in 2013), paediatricians face new challenges in the management of HIV infection, including maintaining treatment adherence.

A range of available drugs is effective in blocking the replication of HIV. They are usually used in a combination of three drugs (sometimes four) and are taken once or twice each day. This combination antiretroviral therapy (ART), the standard of care for > 10 years, suppresses HIV, thus preventing decline in immunological function and the development of associated opportunistic infections, all resulting in marked reductions in morbidity and mortality in HIV-infected children. ART is expensive but is cost-effective (the cheapest first-line regimen cost approximately £7000.00 per annum in 2008). However, there is increasing recognition of the difficulties that young people face in maintaining long-term adherence to treatment regimens. The critical importance of adherence to the long-term success of ART in maintaining virological suppression and preventing the emergence of resistance has been established. However, experience with HIV-infected young people suggests that, with current treatment strategies, adherence rates frequently fall below the 90–95% adherence associated with long-term success. Furthermore, there is increasing recognition of the long-term toxicities of some ART regimens [e.g. efavirenz (EFV)], which is particularly relevant for young people facing lifetime ART, and the associated burden on the NHS.

There is a growing population of young people, pre-adolescents, adolescents and young adults, who face the challenge of long-term adherence to daily ART and for whom better treatment approaches are needed. One possible strategy, relevant for long-acting ART regimens, is to give therapy during the week but allow a break at the weekend. The BREATHER trial aimed to show that, with an EFV-based ART regimen, such a strategy could be effective in maintaining virological suppression, could counteract the trend towards decline in adherence and, importantly, does not lead to an increase in resistance mutations.

Objectives

The primary objective was to determine whether or not EFV-based ART in short cycles of 5 days on and 2 days off (short-cycle therapy; SCT) was as efficacious (in maintaining virological suppression) as continuous EFV-based ART (continuous therapy; CT) in HIV-infected young people aged 8–24 years. Secondary objectives included the occurrence of new clinical HIV events or death, changes in immunological status, emergence of HIV drug resistance, drug toxicity and changes in therapy.

Participants

Inclusion criteria were:

- HIV-1-infected young people aged 8–24 years inclusive, with parents/carers and/or young people, where applicable, willing to provide informed consent.
- On a stable first-line ART treatment regimen containing at least two nucleoside reverse transcriptase inhibitors (NRTIs)/non-nucleoside reverse transcriptase inhibitor (NNRTIs) and EFV for at least 12 months and willing to continue the regimen throughout the study period. Young people on regimens containing nevirapine (NVP) or a boosted protease inhibitor (PI) with undetectable viral load (VL) for > 1 year could be enrolled if they switched to EFV and remained stable with a VL of < 50 copies (twice) for a minimum of 12 weeks. Previous dual therapy and/or substitution of NRTIs was allowed providing any changes were not for disease progression or immunological or virological failure, defined as two successive HIV-1 ribonucleic acid (RNA) results of > 1000 copies/ml, subsequent to virological control having been achieved on ART.
- Viral suppression (HIV-1 RNA < 50 copies/ml) for at least the previous 12 months (at least the last three measurements, including screening); young people who had experienced a single VL blip [> 50 but < 1000 copies/ml (preceded and followed by a VL of < 50 copies/ml) in the last 12 months could be enrolled].
- CD4 cell count of $\geq 350 \times 10^6$/l at the screening visit.
- Clinical centre needed to routinely use an assay that detected a HIV-1 RNA VL of ≥ 50 copies/ml.

Exclusion criteria were:

- pregnancy or risk of pregnancy in females of childbearing potential
- acute illness (young people may be enrolled after illness)
- receiving concomitant therapy for an acute illness (young people may be enrolled after recovery)
- creatinine, aspartate aminotransferase or alanine aminotransferase elevation of grade 3 or above at screening
- on a regimen including NVP or a boosted PI drug (young people could substitute to an EFV-based regimen)
- previous ART monotherapy (except for prevention of mother-to-child transmission).

Methods

Young people were randomised 1 : 1 to either remain on continuous ART or change strategy to a SCT strategy of 5 days on ART and 2 days off.

The first 32 young people randomised were enrolled in an integral pilot study with additional monitoring on a Monday morning (before taking ART) at weeks 1, 2, 3 and 4. The pilot study results were reviewed by the Independent Data Monitoring Committee before young people were enrolled in the main trial.

The trial was managed by three Paediatric European Network for Treatment of AIDS (PENTA) trials units, led by the Medical Research Council Clinical Trials Unit at University College London where data analyses were undertaken. Data were recorded on case report forms and sent to the trials units, entered onto databases and exported into Stata 13.1 (StataCorp LP, College Station, TX, USA) for analysis.

In the main trial, young people were monitored for a minimum of 48 weeks, with scheduled clinic visits at 4 and 12 weeks after randomisation and then every 12 weeks.

The primary outcome (virological failure) was reached if a young person had a confirmed (i.e. twice) VL of ≥ 50 copies/ml. The difference between arms in the proportion of young people reaching the primary end point was calculated at 48 weeks using Kaplan–Meier methods, adjusting for stratification factors (age band; African vs. non-African). A 12% non-inferiority margin was prespecified, so that, if the upper bound of the 90% confidence interval (CI) of the difference in proportion (CT – SCT) was < 0.12, non-inferiority would be demonstrated.

Secondary end points included the occurrence of new HIV Centers for Disease Control (CDC) B or C events or death, a HIV-1 RNA VL of < 50 copies/ml at 24 and 48 weeks, changes in CD4 count and CD4%, emergence of major resistance mutations, evidence of drug toxicity and changes in ART.

Results

In total, 199 young people were enrolled between 1 April 2011 and 28 June 2013. Participants were followed up for a median of 85.7 weeks up to 22 August 2014.

Baseline characteristics

The 199 young people were randomised from 11 countries to SCT ($n = 99$) and CT ($n = 100$). In total, 105 (53%) participants were male and the median [interquartile range (IQR)] age of participants was 14.1 (11.9–17.6) years; 77 participants (39%) were aged 8–12 years, 80 (40%) were aged 13–17 years and 42 (21%) were aged 18–24 years. In total, 70 participants (35%) were recruited from a single centre in Uganda. Overall, 56% of young people were black, 19% were Asian and 21% were Caucasian.

The median (IQR) CD4 count was 735 (575.5–967.5) cells/mm^3 and the median (IQR) CD4% was 34.0% (29.5–38.5%). There were more young people in the CT arm than in the SCT arm with CDC stage C events at baseline (13 SCT vs. 21 CT). All other characteristics were well matched between arms.

All young people were on first-line ART, never having switched for virological failure, although some had had previous regimen changes for simplification or toxicity. Thus, 88 (41%) young people were on their exact initial ART regimen at baseline and 29 (15%) had had previous exposure to a PI.

Of 80 young people completing a baseline acceptability questionnaire, 70 (88%) thought that stopping ART at the weekends would make life easier than CT.

Follow-up

At the end of the main trial, the median (IQR) follow-up time was 85.7 (62.0–118.3) weeks. One young person was lost to follow-up by week 48 (moved to a different country after the week 24 visit). At least 93% of the young people attended every scheduled visit up to week 48.

Primary end point

By week 48, 13 young people reached the primary end point of HIV-1 RNA ≥ 50 copies/ml, six from the SCT arm and seven from the CT arm. The estimated probability of virological failure in the SCT arm was 6.1% and in the CT arm was 7.3%, an estimated difference (SCT – CT) of 1.2% in favour of SCT (90% CI –7.3% to 4.9%). The upper bound of the 90% CI of the difference was 4.9%, well within the non-inferiority margin of 12%. The results are consistent with the non-inferiority of SCT compared with CT.

The analysis was repeated without adjusting for stratification factors and results were qualitatively unchanged (results not shown).

Changes in antiretroviral therapy strategy during the trial

Eight young people on SCT changed strategy to taking drugs 7 days a week during the first 48 weeks: six reached the primary end point, one discontinued EFV because of an adverse event (AE) and one who remained virologically suppressed discontinued for compliance issues.

Adherence

It was important to measure adherence to the randomised arm to ensure that those randomised to SCT stopped ART at weekends and those randomised to CT did not stop ART at weekends. We evaluated this in four ways: self-reported adherence questionnaires; a MEMSCap™ Medication Event Monitoring System (MEMSCap Inc., Durham, NC, USA) substudy in which number of MEMSCap openings were electronically recorded; by investigating haematological mean corpuscular red blood cell volume (MCV) in those taking zidovudine (ZDV) as part of their ART regimen (ZDV is associated with an increase in MCV levels with increased exposure); and self-reported adherence questionnaires.

Analysis of questions on compliance to SCT strategy at follow-up visits showed good compliance, with 95% of weekend breaks being taken in the SCT arm (99% excluding time after return to CT). The MEMSCap substudy was carried out in 61 young people ($n = 31$ SCT group, $n = 30$ CT group), of whom 46 ($n = 23$ SCT group, $n = 23$ CT group) continued to use MEMSCaps throughout the 48 weeks. The median (IQR) number of bottle openings per week was 5 (4–5) for those on SCT compared with 7 (6–7) for those in the CT arm. A significantly higher level of MCV was observed in ZDV recipients randomised to SCT versus CT at each visit ($p < 0.01$); this difference was not observed in young people not on ZDV-containing ART. Self-reported adherence was similar in both arms, with 7% (29/414) reports in the SCT arm versus 10% (40/409) reports in the CT arm of missing ART in the last week (excluding weekend breaks in SCT) ($p = 0.42$).

These four measurements provided strong supportive evidence that participants in each arm were adherent to their randomised strategy as stated in the protocol.

Secondary end points

Of 13 young people ($n = 6$ SCT group, $n = 7$ CT group) reaching the primary end point, resistance results were obtained from nine ($n = 3$ SCT group, $n = 6$ CT group); the remaining four had resistance tests performed but the VL of the sample was too low to obtain a result. Seven young people ($n = 2$ SCT group, $n = 5$ CT group) had major NNRTI mutations at virological failure. In the SCT arm these were L100I + Y188C + K103N and K103N and in the CT arm these were E138A + V106M, K103N + V106M, M230L, V106M + K103N and G190S. Two young people, one from each group, had the M184V NRTI mutation.

The primary analysis was repeated with the end point as a confirmed VL of ≥ 400 copies/ml. Six young people reached this end point ($n = 2$ SCT group, $n = 4$ CT group); the results were consistent with the non-inferiority of SCT.

There were no significant differences between arms in immunological markers (CD4 count, CD4%, CD3 count, CD3%, CD8 count or CD8%). No significant differences were observed between arms with regard to biochemistry, haematology or lipid markers.

Of 90 young people randomised to SCT who completed the end-of-study acceptability questionnaire (completed at the last follow-up visit or at the time of change to CT), 81 (90%) reported that weekend breaks made life a little or a lot easier. The main benefit was going out with friends, which 15 out of 76 young people said was difficult at baseline compared with only two out of 76 at study end ($p = 0.001$).

Safety

There were no new CDC stage C events or deaths and only two CDC stage B events, one in each group. There were 13 serious adverse events in nine young people, seven episodes in six young people in the SCT arm and six episodes in three young people in the CT arm. There were no significant differences between

arms in grade 3 or 4 AEs or treatment-modifying AEs. However, the CT arm had more ART-related AEs (two episodes in two young people on SCT vs. 14 episodes in 10 young people on CT) (Poisson $p = 0.02$ for difference in event rates).

Qualitative substudy results

In the qualitative interviews, participants from both arms discussed their initial anxieties about the impact of SCT on their health and adherence patterns; these anxieties decreased over the early months in the trial. Those randomised to SCT reported an overall preference for SCT over CT pre trial. However, despite overall positive experiences on SCT, young people reported challenges adapting to SCT in the short term. Once they had adapted to the new routine, SCT was reported to reduce the impact of side effects and the pressure to carry and remember medication, thus enabling more weekend activities. Attitudes to SCT did not vary greatly by gender, route of transmission or country. Participants from both arms reported frequent (not easily quantifiable) central nervous system side effects attributed to EFV, and occasional missed doses, which had been difficult to voice to clinic staff. SCT has the potential to encourage more candid discussions about adherence 'slippages' and how treatment demands can be managed alongside their other priorities. Although participants liked SCT by the trial end, they had concerns that peers who had the most problems adhering would also have the most difficulties with managing SCT, with it potentially being disruptive and leading to longer 'slippages'. To realise the potential of SCT and mitigate possible risks, careful dissemination and communication post trial is needed. SCT should be provided as part of a package of monitoring, support and education over 3 months to allow adaptation.

Conclusions

In the BREATHER (PENTA 16) trial after 48 weeks of follow-up, 94% young people remained virologically suppressed and the non-inferiority of SCT compared with CT was demonstrated with only a 1.2% difference in viral suppression to < 50 copies/ml between the arms, in favour of SCT. Primary and secondary analyses were consistent with no significant differences in the secondary end points. Safety profiles were similar between the two strategies, except that there were more ART-related AEs reported in the CT arm. Acceptability questionnaires indicated a strong preference for the SCT strategy compared with CT.

In this Phase II study, the non-inferiority of SCT compared with CT was demonstrated in a select group of virally suppressed, adherent young people on first-line EFV-based ART. These results offer proof of concept that SCT, using at least one antiretroviral (ARV) with a long half-life, can be as effective as daily therapy, resulting in less restriction at weekends and normalising life experiences for young people while reducing overall drug exposure.

A 27% reduction in ARVs needed to maintain viral suppression also has potentially significant cost savings, which might eventually enable even more young people to receive therapy in resource-limited areas.

Importantly, before such a strategy can be more widely adopted, the Trial Management Group, the Trial Steering Committee and the Independent Data Monitoring Committee agreed that review of the results over a longer period of follow-up was required. This has received approval from all ethics committees and is currently under way. In total, 176 out of 194 (90.7%) young people agreed to continue their randomised strategy with follow-up to July 2016. In addition, studies in broader patient populations, with different monitoring strategies and for longer durations, will be required before considering SCT strategies in clinical practice guidelines.

The BREATHER trial was presented as an oral late-breaker presentation at the Conference for Retroviruses and Opportunistic Infections meeting in Seattle, USA, in February 2015. Information has been disseminated to all of the clinical centres participating in the trial, including an information leaflet for young people. The main trial results have been published in *The Lancet* [The BREATHER (PENTA 16) Trial Group. 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 (published online ahead of print 20 June 2016). *Lancet HIV* 2016].

Trial registration

This trial is registered as ISRCTN97755073, EUDRACT 2009–012947–40 and CTA 27505/0005/001–0001.

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