A randomised trial of resistance testing versus no resistance testing in children with virological failure: the PERA (PENTA 8) trial

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Abstract

The development of resistance to antiretroviral drugs is considered to be an important cause of treatment failure in HIV infection. Many randomised trials and studies have been conducted to assess the clinical utility of resistance testing in adults, with mixed conclusions. However, current clinical guidelines recommend the routine use of resistance testing as part of patient management.

HIVART appears to be less successful at reducing HIV RNA to below levels detectable in adults than in adults and adherence may also be more difficult in children, increasing the risk of development of resistance and possible virological failure. ART options are also more limited in children as fewer drugs are licensed and paediatric formulations are not always available. For these reasons, the role of resistance testing in improving virological outcome in children may be different compared with adults.

The objectives of this study were to evaluate the long-term utility of genotypic resistance testing in HIV-infected children with virological failure.

Methods

Trial design and participants

PERA was an open, controlled, 2-arm, parallel-group, multicentre trial. HIV-1-infected children aged 2 to 18 years were eligible if a decision had been made to switch ART therapy due to virological failure, the most recent HIV-1 RNA plasma viral load was >400 copies/mL, and they had been exposed to at least 2 NRTIs for at least 2 years. Children were randomised 1:1 between no resistance testing and access to a genotypic resistance test at the time of randomisation and at any point during follow-up as necessary.

For children randomised to no resistance testing, a new ART regimen was prescribed (randomisation, children allocated to resistance testing had to wait for the results before switching therapy. Follow-up was 12 weeks until the last child randomised had completed 48 weeks; all children were followed to 96 weeks.

Resistance assay

Resistance testing was performed by ViroSeq (Medishen, Belgium) using a genotypic test with computer assisted interpretation (VirtualPhenotype®).

Each test arm showed key drug-associated mutations and the predicted fold-change in IC50 for 16 antiretroviral drugs (including lopinavir/ritonavir and tenofovir) which were added in January 2001.

Expert advice on the interpretation of the report on the new ART regimen was provided as a matter of course, although Steering Committee guidelines would be consulted.

Endpoints

The primary endpoint was change in plasma HIV-1 RNA viral load between baseline (week 0) and 48 weeks. Secondary endpoints included the proportion of children with undetectable viral load (<50 copies/ml) at 48 weeks, change in CD4% and change in immunological response.

Results

Baseline characteristics

170 children were randomised to no testing (68%) or resistance testing (32%) between June 2003 and July 2003 (Table 1).

Children were enrolled from 24 centres in 6 countries: Italy (68 children), Brazil (64), UK (27), Spain (9), Germany (2) and Portugal (1).

In the test arm, resistance was predicted to:
- ZDV and 3TC for 69% and 77% if samples
- ddI and 3TC for 19% and 13% if samples
- NVP, RTV and ddI for 35%, 49% and 48% of samples
- NVP and ddI for 35%, 26% and 21% (only 46 samples were tested before January 2001) for LPV use (see Methods)

There were no significant differences between the arms in terms of:
- number of drugs in the test regimen
- specific NRTI and PI drugs in the new regimen

There were differences in the NRTIs prescribed:
- ddI and 3TC were prescribed significantly more frequently together and alone in the test arm
- 56% of children in the test arm were prescribed ddI+3TC as their new RTI backbone compared to 19% in the no test arm (p=0.01)

The mean (SD) CD4% increase at week 48 was 1.7% (0.9) in the no test arm and 3.5% (2, 6) in the test arm, and 29% observed a substantial effect on NRTI prescribing patterns.

Immunological response

The mean (SD) CD4% increase at week 48 was 1.7% (0.9) in the no test arm and 3.2% (0.9) in the test arm, a difference of 1.6% (95% CI: 0.8% to 4.0%, p-0.02).

Discussion

In this first paediatric trial of resistance testing, we observed a substantial effect on NRTI prescribing patterns.

We thank all the children, families and staff from the centres participating in the PERA (PENTA 8) Trial.

We also thank Vince (Mechelen, Belgium) for providing resistance testing for children in the test arm.