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

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Background/Objectives

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.

HAART appears to be less successful at reducing HIV RNA to below levels of detection in children than 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 objective of this study was to evaluate the longer-term utility of genotypic resistance testing in HIV-infected children with virological failure.

Methods

Trial design and participants

PERA was an open, randomised, 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 exceeded 2000 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 at randomisation; children allocated to resistance testing had to wait for the results before switching therapy.

Follow-up was 12-weekly until the last child randomised had completed 48 weeks; all children were followed to 96 weeks.

Resistance assay

Resistance testing was performed by VIRCO (Mechelen, Belgium) using a genotypic test with computer assisted interpretation (VirtualPhenotype™).

Each test report showed key drug-associated mutations and the predicted fold-change in IC_{50} for 16 antiretroviral drugs (including lopinavir (LPV) and tenofovir (TDF) which were added in January 2001).

Expert advice on the interpretation of the report or on the new ART regimen was not provided as a matter of course, although Steering Committee virologists could 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%, change in antiretroviral treatment prescribed after randomisation and progression to new AIDS defining events or death.

Baseline characteristics

- 170 children were randomised to no testing (n=83) or resistance testing (n=87) between June 2000 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% of samples
  - ddI, d4T and ABC for 19%, 29% and 43% of samples
  - NVP and EFZ for 31% and 24% of samples
  - NFV, RTV and IDV for 55%, 49% and 48% of samples
  - APV and LPV for 26% and 25% (only 40 samples after January 2001 tested for LPV resistance (see Methods))

Table 1: Baseline characteristics

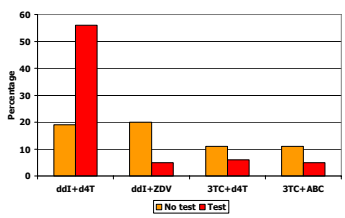
	No test (N=83)	Test (N=87)
Previous resistance test	4%	8%
Male	54%	55%
Age (years)		
0 to 6	31%	36%
7 to 10	29%	36%
11 or older	40%	29%
Ethnic origin		
white / black African / other	54 / 18 / 11	57 / 20 / 10
CDC disease stage C	41%	28%
Mean (SD) HIV-1 RNA (log_{10} c/ml)	4.7 (0.9)	4.7 (0.9)
Mean (SD) CD4%	21 (11)	20 (9)
Previous ART exposure		
NRTIs only	10%	17%
NRTIs+NNRTIs	7%	11%
NRTIs+PIs	54%	52%
NRTIs+NNRTIs+PIs	29%	20%
Mean (range) number of drugs received		
All	5.2 (2, 10)	4.7 (2, 11)
NRTI	3.5 (2, 6)	3.2 (2, 5)
NNRTI	0.4 (0, 2)	0.4 (0, 3)
PI	1.3 (0, 3)	1.1 (0, 4)
Mean (range) cumulative ART exposure (years)	5.2 (1, 13)	5.0 (0, 12)
First ART regimen		
mono/dual	82%	70%
triple	18%	30%

New ART regimen

Drugs prescribed

- There were no significant differences between the arms in terms of:
  - drug classes in the new regimen
  - number of drugs in the new regimen
  - specific NNRTI and PI drugs in the new regimen
- There were differences in the NRTIs prescribed:
  - ddI and d4T were prescribed significantly more frequently alone and together in the test arm
  - 56% of children in the test arm were prescribed ddI+d4T as their new NRTI backbone compared to 19% in the no test arm (Figure 1)
  - ZDV, 3TC and ABC were prescribed less frequently in the test arm

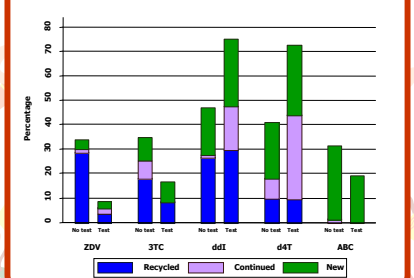
Figure 1: NRTI backbones prescribed after randomisation



New, continued and recycled drugs

- There was no significant difference in the number of new (never used before) drugs prescribed between the arms, overall or within class.
- There were however differences in the number of NRTIs continued from baseline or recycled from previous regimens (Figure 2):
  - 49% children continued 1 or more NRTIs from the baseline regimen in the test arm compared to 19% in the no test arm (p<0.01)
  - more children in the no test were prescribed drugs from previous regimens (55% in no test arm recycled 1 or more drugs vs 43% in test arm, p<0.01)
  - ddI and d4T were predominantly continued in the test arm, whereas ZDV and 3TC were recycled in the no test arm

Figure 2: NRTIs recycled, continued or new



Planned versus prescribed regimens

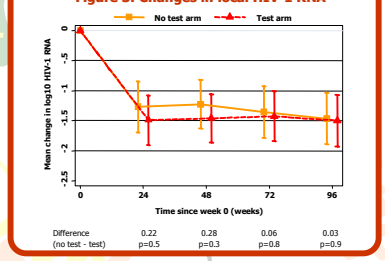
- Clinicians were asked at the screening visit:
  "If randomised to no resistance testing, what regimen you would prescribe today?"
- 82% prescribed at least one drug differently to this planned regimen in the test arm compared to only 18% in the no test arm (p<0.001).
- In the test arm, 48 out of 84 (57%) children were prescribed a regimen containing all "sensitive" drugs, according to the VirtualPhenotype™

Virological & immunological response

Virological response

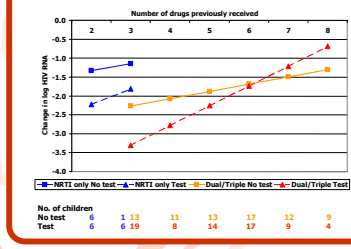
- The mean (SE) reduction in HIV-1 RNA at 48 weeks was 1.23 (0.20) log_{10} copies/ml in the no test arm compared with 1.51 (0.20) in the test arm, a difference of 0.28 (95% CI: -0.84 to 0.28, p=0.3).
- The difference between the arms was smaller at week 96 (Figure 3).
- There was no significant difference between the proportion of children with a viral load <50 copies/ml at 48 (no test arm 19%, test arm 21%, p=0.8) or 96 weeks (no test arm 21%, test arm 18%, p=0.7).

Figure 3: Changes in local HIV-1 RNA



- Exploratory analysis revealed an interaction between number of drugs previously received & arm (p=0.01), and class of drugs previously received & arm (p=0.07) (Figure 4).
- Excluding children who had only ever received NRTIs, the test arm did better compared to the no test the fewer drugs previously received.
- No differences in PI & NNRTI drugs prescribed ⇒ possible impact of differences in NRTI prescribing on virological response
- In the test arm, ddI & d4T were consistently shown as "sensitive" on the test reports and prescribed more frequently. These drugs are less likely to be sensitive with more prior exposure and this may explain the effect on virological response

Figure 4: Change in HIV-1 RNA at 48 weeks



Immunological response

- The mean (SE) 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=0.2).
- The difference had increased at week 96 to 2.5% (95%CI: -0.1 to 5.2, p=0.06).

Summary

- In this first paediatric trial of resistance testing, we observed a substantial effect on NRTI prescribing patterns.
- However there was no clear evidence of a virological or immunological benefit.
- Resistance testing without expert interpretation is likely to provide at most marginal gains in virological outcomes.
- Better ways to interpret resistance tests and strategise their use are needed.

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