Poster Board No.
898

HIV-1 resistance after randomized virologic switch at 1,000 or 30,000 c/ml in children

Linda Harrison[1], Diana Gibb[2], Susan Fiscus[3], Yacine Saidi[4], Eleni Nastouli[5], Lynda Harper[2], Alexandra Compagnucci[4], Abdel Babiker[2], Ann Melvin[6], Gareth Tudor-Williams[7], and the PENPACT 1 (PENTA 9/PACTG 390) Study Team

[1]Center for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, MA, [2]Medical Research Council, Clinical Trials Unit, London, UNITED KINGDOM, [3]UNC-Chapel Hill Virology Laboratory, UNC School of Medicine, Chapel Hill, NC, [4]INSERM, SC10, Paris, FRANCE, [5]University College Hospital, University College London, London, UNITED KINGDOM, [6]Seattle Children's Hospital, Seattle, WA, [7]Imperial College London, London, UNITED KINGDOM

Linda Harrison
Harvard School Of Public Health
651 Huntington Ave.
FXB 600A
Boston, MA 02115
617-432-0062
lharriso@sdac.harvard.edu

ABSTRACT

Background: There are no comparisons of resistance after randomized virologic switch criteria.

Methodology: PENPACT 1 was an international open label 2 by 2 factorial trial randomizing HIV infected children to start antiretrovirals with a protease inhibitor (PI) vs non nucleoside reverse transcriptase inhibitor (NNRTI) based regimen, and switch at RNA threshold of 1000 vs 30000 c/ml. Switch criteria were: not achieving the threshold by week 24, confirmed rebound above the threshold after week 24 (RNA tested 12 weekly), or CDC C event. Resistance testing was on the last sample ≥1000 c/ml before switch, or confirmed ≥1000 c/ml before re-suppression; to ensure fair comparison by 1000 and 30000 arms. Additional testing was on samples ≥1000 c/ml at 4 years and trial end. This secondary analysis tested differences in number of major IAS mutations by Poisson models.

Results: Of 263 children, 67 started PIs and were assigned the 1000 threshold (PI 1000), 64 PI 30000, 67 NNRTI 1000 and 65 NNRTI 30000. Half on PIs started lopinavir/ritonavir, 62% on NNRTIs efavirenz (**Table 1**). The 1000 criteria were reached by 94 (36%) children during median 5.0 (IQR 4.2-6.0) years follow-up. Time to reaching the 1000 criteria was similar by class (log rank P 0.26). Most in the 1000 arm reaching the criteria switched soon after (PI vs NNRTI median 12 vs 8 wks, log rank P 0.60). Median weeks from 1000 to 30000 criteria was 80 for the 30000 arm; PI vs NNRTI 58 vs 80, log rank P 0.81, and 25% of children had switched by 44 weeks; PI vs NNRTI 63 vs 17, log rank P 0.16. 87/107 (81%) children with last sample ≥1000 c/ml had resistance test results. Median weeks from entry to last test was 96; 1000 vs 30000 72 vs 124, rank sum P<0.01. More NRTI resistance mutations were accumulated in NNRTI 30000 than the other arms (**Table 1**). More NNRTI than PI mutations were accumulated; NNRTI mutations were frequent in 1000 and 30000, and PI resistance was less common in both arms. For non-randomized NRTIs, 62 started ABC+3TC, 166 3TC+ZDV/d4T, and 35 other (25 ZDV+ddI). The ABC+3TC group had fewer mutations than the others. The 5 with mutations on ABC+3TC were on NNRTIs; all had M184V/I and 1 K65R, L74V, Y115F, while 22/39 3TC+ZDV/d4T were on NNRTIs; all had M184V/I and 10 had TAMs.

Conclusions: Children starting PIs tended to switch later spending longer above 1000 but accumulated fewer mutations. Children starting NNRTIs switched soon after the 30000 criteria and accumulated more mutations, particular to NRTIs. An ABC+3TC backbone seemed most protective against NRTI resistance.

BACKGROUND

PENPACT-1 is the only long-term strategy trial in children or adults to assess which ART regimen to start (PI vs. NNRTI) and when to switch to 2nd line ART based on RNA thresholds [1]. Guidelines recommend switching at a confirmed RNA >1000 c/ml, but direct evidence for this threshold remains weak [2].

We explored the resistance profiles after 1st line ART for children in the PENPACT-1 trial, and assessed the impact of randomly assigned virologic switch criteria on 2nd line options.

METHODS

PENPACT-1 randomized:
- 263 HIV-infected ART-naive children aged between 0 and 18 years from Europe and North and South America from 2002 to 2005 to the 4 groups in **Figure 2**

1st line ART:
- initial regimen chosen by the treating clinician according to randomized class (PI or NNRTI), plus any drug substitutions for non-virologic reasons (e.g. toxicity)

Switch to 2nd line ART:
- if not achieved randomized RNA threshold (1000 or 30000 c/ml) by week 24
- confirmed rebound at/above RNA threshold (1000 or 30000 c/ml) after week 24
- a new CDC stage C event

For analysis:
- **1000 criteria** = not achieved <1000 c/ml by week 24, confirmed rebound ≥1000 c/ml at/after 24 weeks, or a new CDC stage C event.
- **30000 criteria** = not achieved <30000 c/ml by week 24, confirmed rebound ≥30000 c/ml at/after 24 weeks, or a new CDC stage C event.

Resistance testing on 1st line:
- last sample with RNA ≥1000 c/ml before switch
- last sample at confirmed RNA ≥1000 c/ml (e.g. if not switched because 30000 criteria not met by trial end)
- sample with RNA ≥1000 c/ml at 4 years or trial end

Resistance analysis:
- Major resistance mutations according to IAS criteria were accumulated on 1st line
- Differences were tested by Poisson regression assuming children not fulfilling criteria for testing did not develop mutations
- 2nd line ART options were assessed by Stanford susceptibility score

RESULTS

Figure 2: Study Design and Major Resistance Mutations Accumulated on 1st line ART

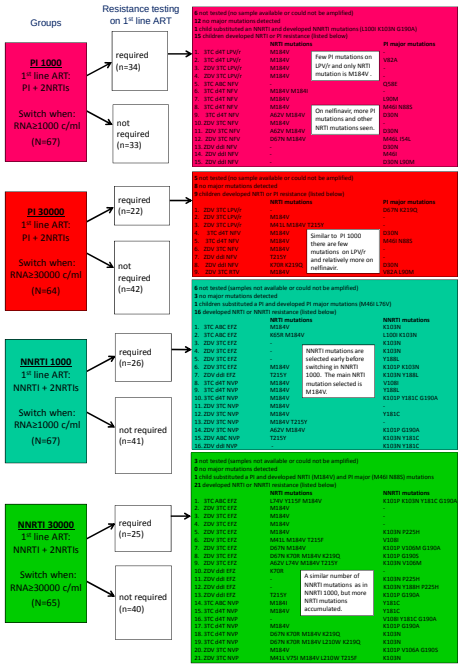


Figure 1: Time from 1000 to 30000 criteria and switch for 43/129 (33%) children reaching the 1000 criteria in the 30000 group

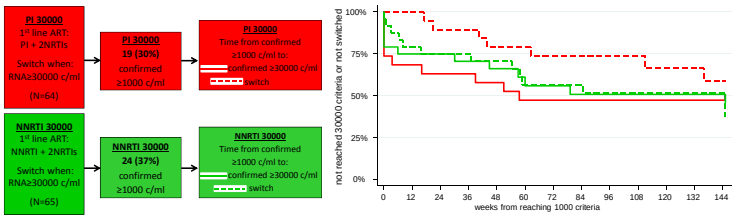


Table 1: Major IAS Resistance Mutations Accumulated on 1st line ART

	PI 1000	PI 30000	NNRTI 1000	NNRTI 30000	Poisson P-value*
Total children	**67**	**64**	**67**	**65**	
Lopinavir/ritonavir	29 (43%)	36 (56%)	0 (0%)	0 (0%)	
Nelfinavir	37 (55%)	27 (42%)	0 (0%)	0 (0%)	
Other**	1 (1%)	1 (2%)	0 (0%)	0 (0%)	
Efavirenz	0 (0%)	0 (0%)	43 (64%)	39 (60%)	
Nevirapine	0 (0%)	0 (0%)	24 (36%)	26 (40%)	
Number requiring tests	34	22	26	25	
Number with test results	28	17	20	22	
NRTI resistance					
1 or 2 mutations	11 (18%)	7 (12%)	12 (20%)	12 (19%)	any difference
≥3 mutations	0 (0%)	1 (2%)	0 (0%)	7 (11%)	<0.001
PI or NNRTI resistance					
1 or 2 mutations	10 (16%)	4 (7%)	13 (21%)	12 (19%)	PI vs NNRTI
≥3 mutations	0 (0%)	0 (0%)	1 (2%)	5 (8%)	<0.001

	ABC+3TC	3TC+ ZDVId4T	Other (mainly ZDV+ ddI)	Poisson P-value*
Total children	**62**	**166**	**35**	
Number requiring tests	15	67	25	
Number with test results	9	59	19	
NRTI resistance				
1 or 2 mutations	4 (7%)	32 (20%)	6 (21%)	any difference
≥3 mutations	1 (2%)	7 (4%)	0 (0%)	<0.01
Thymidine analogue mutations (TAMs)				
1 or 2 TAMs	0 (0%)	6 (4%)	6 (21%)	
≥3 TAMs	0 (0%)	4 (3%)	0 (0%)	
K65R	1 (2%)	0 (0%)	0 (0%)	
L74R	1 (2%)	1 (1%)	0 (0%)	
Y115F	1 (2%)	0 (0%)	0 (0%)	
M184V/I	5 (9%)	39 (25%)	0 (0%)	

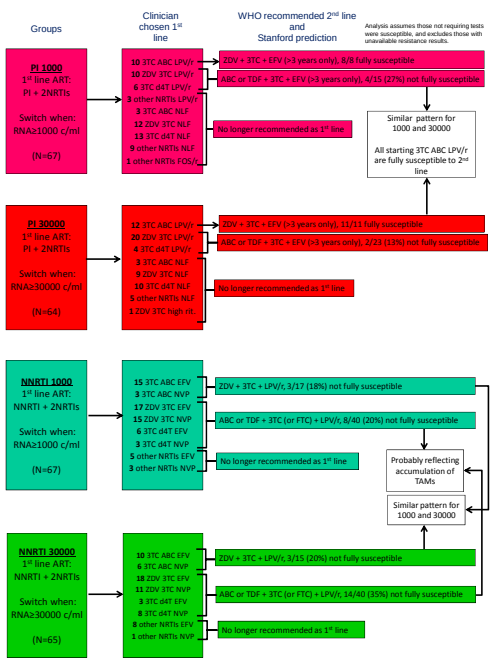
* Analysis assumes those not requiring tests were not resistant, and excludes those with unavailable resistance results.
** 1 fosamprenavir/ritonavir, 1 high-dose ritonavir

Figure 1 displays the time from 1000 to 30000 criteria and switch:
- Of 263 children, 94 (36%) reached the 1000 criteria over ~5 years
  - 51 (38%) randomized to switch at 1000 c/ml (1000 group)
  - 43 (33%) randomized to switch at 30000 c/ml (30000 group)
- The 43 reaching the 1000 criteria in the 30000 group are displayed in figure 1.
- It took a median of 80 weeks from the 1000 criteria to the 30000 criteria.
- Children on PIs reached the 30000 criteria slightly earlier than those on NNRTIs, but switched to 2nd line slightly later.
- Children on NNRTIs switched immediately after the 30000 criteria were met.

Figure 2 and **Table 1** display the number of children requiring resistance tests and major resistance mutations accumulated:
- More NNRTI than PI mutations were accumulated
- NNRTI mutations accumulated quickly, with similar frequency in both NNRTI 1000 and NNRTI 30000.
- PI resistance was less common in both PI 1000 and PI 30000, especially on LPV/r.
- More NRTI mutations were accumulated in NNRTI 30000 than the other groups; more children with ≥3 NRTI mutations in NNRTI 30000 drove this difference
- Those on non-randomized NRTIs ABC+3TC developed fewer mutations than the other NRTI combinations.

Figure 3 displays susceptibility scores to potential 2nd line ART:
- All children on 1st line 3TC+ABC+LPV/r were susceptible to 2nd line ZDV+3TC+EFV in PI 1000 and PI 30000
- 4 (27%) and 2 (13%) in PI 1000 and P1 30000 were not fully susceptible to 2nd line after 1st line ZDV or d4T+3TC+LPV/r
- After 1st line 3TC+ABC+NNRTI, 3 (18%) and 3 (20%) in NNRTI 1000 and NNRTI 30000 were not fully susceptible to 2nd line ZDV+3TC+LPV/r.
- After 1st line ZDV or d4T+3TC+NNRTI, 8 (20%) and 14 (35%) in NNRTI 1000 and the NNRTI 30000 were not fully susceptible to 2nd line ABC or TDF+3TC (or FTC)+LPV/r. This likely reflects accumulation of TAMs on ZDV or d4T.

Figure 3: 2nd line ART Options



CONCLUSIONS

- Children starting NNRTIs randomized to switch at 30000 c/ml switched promptly after the 30000 criteria were met, but accumulated more mutations. In particular, more NRTI mutations accumulated. NNRTI mutations appeared in similar frequency in both the 1000 and 30000 groups.
- Children on PIs tended to switch later spending longer ≥1000 c/ml, but, despite this, fewer major mutations accumulated; particularly on LPV/r.
- These data confirm the protective effect of LPV/r against accumulation of NRTI and PI resistance.
- When ABC+3TC was prescribed with LPV/r resistance did not occur, and when prescribed with an NNRTI 2nd line susceptibility was similar in the 1000 and 30000 groups
- When ZDV or d4T+3TC was prescribed with LPV/r 2nd line susceptibility was similar in 1000 and 30000, but when prescribed with an NNRTI, fewer children in the 30000 group were susceptible to recommended 2nd lines. This is likely due to accumulation of TAMs on ZDV or d4T+3TC when combined with an NNRTI.
- Therefore, non-randomized analysis suggests ABC+3TC as the 1st line NRTI backbone results in less resistance than ZDV or d4T+3TC for both LPV/r and NNRTIs.

REFERENCES

1. PENPACT-1 (PENTA 9/PACTG 390) Study Team, Babiker A, Castro nee Green H, Compagnucci A, Fiscus S, Giaquinto C, Gibb DM, Harper L, Harrison L, Hughes M, McKinney R, Melvin A, Mofenson L, Saidi Y, Smith ME, Tudor-Williams G, Walker AS. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. Lancet Infect Dis. 2011 Apr;11(4):273-83. doi: 10.1016/S1473-3099(10)70313-3. Epub 2011 Jan 31
2. World Health Organization. Consolidated guidelines on the use of antiretrovirals for the treatment and prevention of HIV infection. 2013. (Accessed Feb 3, 2014, at http://www.who.int/hiv/pub/guidelines/arv2013/download/en/index.html.)

ACKNOWLEDGEMENTS

We thank all the children, families and staff from the centers participating in the PENPACT-1 (PENTA 9/PACTG 390) trial