TITLE PAGE

Outcomes after viral load rebound on first-line antiretroviral therapy in HIV-infected children in the UK/Ireland: an observational cohort study

5 keywords: HIV, antiretroviral therapy, children, second line therapy, viral load rebound

Running title: Switch to second-line ART in children

Authors:

Tristan CHILDS[a], Delane SHINGADIA[b] , Ruth GOODALL[a], Katja DOERHOLT[a], Hermione LYALL[c], Trinh DUONG[a], Ali JUDD[a], Di M GIBB[a], Intira Jeannie COLLINS[a] on behalf of the CHIPS Steering Committee.

Affiliations:

a MRC Clinical Trials Unit at University College London, UK

b Great Ormond Street Hospital for Children NHS Foundation Trust, UK

c Imperial College Healthcare NHS Trust, UK

Author preferred degree and institution addresses

Tristan Childs	MSc
Delane Shingadia	MD
Ruth Goodall	PhD
Katja Doerholt	MD
Hermione Lyall	MD
Trinh Duong	MSc
Ali Judd	PhD

Prof Di M Gibb MD

Intira Jeannie Collins PhD

MRC Clinical Trials Unit at University College London

Institute of Clinical Trials & Methodology

London

England

Great Ormond Street Hospital for Children NHS Foundation Trust

London

England

Imperial College Healthcare NHS Trust

London

England

Corresponding author:

Intira Jeannie Collins

MRC Clinical Trials Unit at UCL

Aviation House, 125 Kingsway, London WC2B 6NH

E: jeannie.collins@ucl.ac.uk T: +44 20 7670 4767

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ABSTRACT

Background: Approximately one-third of HIV-infected children experience virological failure within two years of initiating antiretroviral therapy (ART). We determined the probability of switch to second-line ART or viral load (VL) re-suppression without switch among children who experienced VL rebound on first-line ART in an observational cohort in the UK/Ireland.

Methods: Children with VL rebound (confirmed VL>400c/ml following suppression <400c/ml) on first-line ART were included. Competing risk analysis estimated the probability of: switch to second-line; confirmed re-suppression (two consecutive VL<400c/ml) without switch; and continued VL>400c/ml without switch. Predictors of time to switch were assessed.

Findings: Of 900 children starting first-line ART who had VL<400c/ml by one year, 170 (19%) experienced VL rebound by median [IQR] 20·6 months [9·7-40·5]. At rebound, median age was 10·6 years [5·6-13·4], VL 3·6 $\log_{10}$c/ml [3·1-4·2], and CD4% 24 [17-32]. Eighty-nine (52%) switched to second-line ART at median 4·9 months [1·7-13·4] after VL rebound, 53 (31%) re-suppressed without switch (61% of those on PI-based and 24% of those on NNRTI-based first-line regimens), while 28 (16%) neither re-suppressed nor switched. At 12 months after rebound, probabilities of switch or re-suppression without switch were 38% (95% CI 30-45) and 27% (95% CI 21-34), respectively. Faster time to switch was associated with higher VL (p<0·0001), later calendar year (p=0·02) at VL rebound, and NNRTI- or triple NRTI- versus PI-based first-line (p=0·001).

Interpretation: One-third of children with VL rebound re-suppressed without switch. The possibility of re-suppression with adherence support should be considered prior to switching.

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PANEL

Systematic review

We searched PubMed using the terms “HIV”, “antiretroviral therapy”, “switch”, “second line” and “children”. We identified 17 publications with data on children from a variety of settings which analysed either long-term virological patient outcomes[1,3,4,13,25], durability of first-line ART [2,9,18,19,22] or response to second-line ART[8,23,24,26-29]. Only two studies have reported outcomes following viral load rebound and the probability of switch or resuppression without switch in routine care[19,22].

Interpretation

Our study adds to the evidence about patient outcomes following viral load rebound on first-line antiretroviral therapy. Our well-established cohort contains ~900 HIV-infected children initiated on combination therapy, with median follow up of 5·4 years after start of ART. We analysed the patient outcomes of the 19% of children with confirmed viral rebound, of whom half switched to second-line ART. However, a further third re-suppressed without switch to second line treatment, including 25% of children on NNRTI- and 61% on PI-based first line regimens. Children with lower CD4%, higher viral load, on NNRTI-based regimens at time of virological rebound, and those rebounding in later calendar years were more likely to switch. The possibility of re-suppression, which is comparable to that seen in adults[20], should be considered prior to treatment switch; adherence counselling, dosing review and resistance testing can be used to inform patient management.

INTRODUCTION

The aim of combination antiretroviral therapy (ART) in HIV-infected children is to achieve sustained viral suppression, immune reconstitution and to prevent disease progression. Several papers report that within two years of first-line ART initiation, 33-38% of children experience virological failure; this varies with age and type of first-line ART[1-4]. This has raised concerns regarding the sustainability and long-term treatment options for children, who are recommended immediate ART from infancy and will require lifelong treatment but are faced with a limited range of antiretrovirals available in paediatric formulations[5, 6]. Current guidelines recommend adherence support following raised viral load (VL) and switch to second-line ART if confirmed VL rebound within 6 months, particularly for children on non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens due to the low genetic barrier to resistance and risk of rapid accumulation of resistance in these patients[5-7]. However, the threshold for defining VL failure and optimal timing of switch to second-line ART are less clear. To date, only one trial has compared thresholds for switch in children, the PENPACT-1 trial where children who switched at VL rebound at ≥1,000c/ml versus ≥30,000c/ml (over median time 60 months) showed no difference in VL suppression at four years by this randomisation, nor by the concurrent randomisation to protease inhibitor (PI) or NNRTI-based regimens. Delayed switching on NNRTI-based ART increased nucleoside reverse transcriptase inhibitor (NRTI) but not NNRTI resistance (with the latter occurring rapidly after VL rebound ≥1,000c/ml). PENPACT-1 highlighted the more forgiving nature of boosted PIs compared to NNRTIs; the authors concluded that delayed switching on PI-based ART may be reasonable where future drug options are limited as the risk of development of PI resistance or NRTI thymidine analogue mutations **(**TAMS) was minimal, which has been observed in other studies[8-12]. Treatment guidelines stress the need for adherence counselling, attention to medication intolerance and pharmacokinetic/dosing

issues, as well as confirmation of VL rebound before switching, in order to maximise durability of first-line and response to second-line ART[6].

However, there are scarce data on the 'real-life' management and outcomes following virological failure on first-line ART, which would help inform both the timing and threshold for switching following VL rebound in HIV-infected children. We therefore assessed the probability of switch to second-line therapy or resuppression without switch among children who experienced confirmed VL rebound >400c/ml on first-line therapy within the Collaborative HIV Paediatric Study (CHIPS) in UK and Ireland.

METHODS

CHIPS is a multi-centre cohort study of all HIV-infected children receiving paediatric HIV care in the UK and Ireland, as described elsewhere[13]. In brief, all children presenting in the UK or Ireland with HIV infection or born to HIV-infected mothers are reported to the National Study of HIV in Pregnancy and Childhood (NSHPC); follow-up data on HIV-infected children are collected through CHIPS annually. Children with no reported clinic visit for ≥24 months were considered lost to follow up, to allow for the delays in reporting. Both studies are approved by NHS Research Ethics Committees.

The inclusion criteria for these analyses were: antiretroviral naïve (except neonatal prophylaxis for prevention of mother-to-child transmission (pMTCT)), age under 18 years at initiation of ART with at least three drugs (excluding unboosted PI or triple NRTI-based regimens not containing abacavir) started since 1996; and ≥1 viral load measurement within 12 months of initiating ART. Patients were excluded if they: (1) initiated ART with a NRTI backbone combination of stavudine with didanosine or stavudine with zidovudine as guidelines recommend against combined use of these drugs[7]; (2) had participated in a clinical trial of treatment interruption and/or switching strategies (PENTA-11 or PENPACT1); (3) were on a treatment interruption at the time of VL rebound; (4) switched while virologically suppressed (because the outcomes of interest all occur after VL rebound); (5) aged >18 years at VL rebound.

We first included all children who achieved virological suppression <400c/ml after initiating first-line ART. Following suppression, confirmed VL rebound was defined as two consecutive VL measurements ≥400c/ml within six months of each other. Viral load measurements were routinely taken at three to six monthly intervals in most clinics and the VL ≥400 c/ml threshold was considered the most relevant to clinical care in the UK/Ireland. Data on patients were matched with the UK HIV Drug Resistance Database[14] data from 1996-2012

using an algorithm matching key variables available in both datasets i.e. date of birth, soundex code, gender, initials, clinic etc.

Following confirmed VL rebound, switch to second-line ART was defined as: changing ≥3 drugs simultaneously irrespective of reason; or changing ≥2 drugs for documented treatment failure (virological, immunological, clinical with or without resistance test); or changing 1 drug cross-class for documented treatment failure; or adding a drug from a new class to the regimen.

Following VL rebound the outcomes of interest were: switch to second-line therapy; confirmed resuppression <400 c/ml (two consecutive samples) without switch; and neither switched nor resuppressed. Children were at risk from the date of first VL rebound to the earliest date of switch to second-line ART, confirmed resuppression without switch, death, or most recent clinic visit.

Statistical methods

To avoid overestimation of the cumulative incidence of switch, which is a potential problem when competing events are not independent of one another[15, 16], we used competing risk analysis. Using the model proposed by Fine and Gray[15], we calculated the cumulative incidence of the three outcomes: switch to second-line therapy, confirmed resuppression without switch, and neither switching nor resuppressing following VL rebound. In each model the competing risks were the two alternative outcomes and death. Potential risk factors for earlier switching were gender, first-line regimen, age and CD4% at ART initiation and age, CD4%, VL, duration on ART, and calendar year at VL rebound. The initial regimen was categorised as boosted PI+NRTI, EFV+2NRTI, NVP+2NRTI, NNRTI+3NRTI and 3NRTI. A NNRTI+3NRTI regimen, also referred to as “baby cocktail” is prescribed in some UK clinics for infants <12 months[17]. Calendar year of rebound was categorised to broadly reflect

availability of new antiretroviral drugs as 1996-2003, 2004-2007 and 2008 onwards, with the latter period seeing the introduction of newer PIs (e.g. darunavir and atazanavir) used for first and second line regimens. A priori factors age and calendar year at VL rebound were included in all models. Models were built using backwards elimination (exit probability p>0·1), sub-hazard ratios were reported from the final model (adjusted sub-hazard ratios). Sensitivity analyses were carried out with higher thresholds for VL rebound, defined as confirmed VL ≥1,000c/ml and ≥5,000c/ml after previous suppression.

Analyses are based on data reported to CHIPS to November 2013 and were performed using STATA version 13 (StataCorp, College Station, Texas).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Of 1,843 patients ever reported to CHIPS, 900 suppressed to VL <400c/ml within a year of starting ART (Figure 1). The median [IQR] age and CD4% at ART initiation were 7·9 years [3·1-11·9] and 15% [9-20] and median duration of follow up was 7·8 years [5·0-10·8] after first presentation. Of all eligible patients, 416 (46%) were male, two-thirds (70%) initiated first-line ART since 2003 and three-quarters (76%) initiated on NNRTI-based regimens (Table 1).

Of the 900 patients who achieved VL suppression <400c/ml within 12 months of starting ART, 170 (18%) subsequently experienced VL rebound at median [IQR] 20·6 months [9·7-40·5] after ART initiation (Table 1). The median age, viral load, CD4 count, and CD4% at VL rebound were 10·6 years [5·6-13·4], 3·6 $\log_{10}$ c/ml [3·1-4·2], 550 cells/µl [310-930], and 24% [17-32], respectively, and three-quarters of children initiated on a NNRTI-based regimen. Fifty one (30%) had already experienced some ART modifications not meeting the definition of switch prior to VL rebound. There were no deaths, three patients (2%) were lost to follow up and three experienced new/recurring CDC B or C events (two switched and one resuppressed without switch).

Figure 2 shows the cumulative incidence of switch, resuppression without switch, and neither resuppressing nor switching following VL rebound. By 12 months following VL rebound, an estimated 38% of patients (95% confidence interval [CI] 30-45%) switched to second-line therapy, increasing to 48% (95% CI 40-55%) by 24 months. By 12 and 24 months after VL rebound, an estimated 27% (95% CI 21-34%) and 31% (95% CI 24-38%) of patients resuppressed without switch, whilst the remaining 35% (95% CI 28-42%) and 22% (95% CI 16-29%) of patients neither resuppressed nor switched.

Time to switch

In multivariate analyses, faster time to switch was independently associated with lower CD4% [adjusted sub-hazard ratio (aSHR): 0·89 per 5% increase (95% CI 0·78-1·01), p=0·07] and higher VL [aSHR: 1·88 per $\log_{10}$ c/ml increase (95% CI 1·39-2·55), p<0·0001] at time of VL rebound (Table 2). There was evidence of patients initiated on PI-based regimens being slower to switch [aSHR: 0·13 (95% CI 0·05-0·38)] and a suggestion of faster switch in children on 4-drug NNRTI-based regimens [aSHR: 1·78 (95% CI 0·81-3·92)] when compared to 3-drug efavirenz-based regimens (global p=0·001). There was also evidence to suggest that patients experiencing VL rebound in later calendar years were faster to switch compared with patients who failed in earlier calendar years (p=0·02).

Sensitivity analysis of increasing the threshold of VL rebound

In sensitivity analyses, increasing the threshold of VL rebound to 1,000c/ml and 5,000c/ml resulted in fewer patients meeting the definition of VL rebound (139 and 84 respectively), of whom a higher proportion switched to second-line and a lower proportion resuppressed without switch. By 12 months following VL rebound at 1,000c/ml and 5,000c/ml, an estimated 43% (95% CI 34-51%) and 52% (95% CI 41-62%) switched to second-line, while 24% (95% CI 17-31%) and 15% (95% CI 8-23%) resuppressed without switch, respectively. At the higher VL rebound threshold of 1,000c/ml, 13 (54%) and 24 (22%) patients who initiated on PI-based and NNRTI-based regimens, re-suppressed without switch; at the increased VL rebound threshold of 5,000c/ml, 5 (42%) and 11 (16%) re-suppressed without switch respectively

Patients who switched to second-line therapy

Eighty-nine (52%) patients switched to second-line therapy at median 4·9 months [1·7-13·4] after VL rebound. Of patients who initiated on PI-based and NNRTI-based regimens, 5

(16%) and 76 (59%) switched to second-line therapy, respectively. Eighty two (92%) patients switched to receive a PI-based second line regimen, of whom 62 (76%) switched to lopinavir, 13 (16%) atazanavir, 6 (7%) darunavir and 1 (1%) fosamprenavir At 12 and 24 months after switch to second-line ART, an estimated 85% (95% CI 75-91) and 73% (95% CI 62-82) of patients remained continuously suppressed <400c/ml, respectively.

Patients who experienced confirmed resuppression

Fifty-three (31%) patients resuppressed <400c/ml without switching to second-line therapy, at median 7·4 months [IQR 3·4-10·1] after VL rebound. Of these, nine (17%) made ART changes which did not meet the definition of switch and 44 (83%) made no ART changes; although 10/44 (23%) had a change in dose in line with growth. Of patients who initiated on PI-based and NNRTI-based regimens, 19 (61%) and 31 (24%) resuppressed without switching, respectively. Among the 44 patients who resuppressed with no ART changes, 17 (39%) remained suppressed through to their most recent follow up visit (median 28·5 months [6·8-44·5] after VL rebound) and 27 (61%) had a further episode of virological failure (viral load ≥400c/ml) at median 12·6 months [5·3-25·1] after initial resuppression, of which 9/27 (33%) subsequently switched to second-line therapy at median 20·8 months [8·8-45·1] after initial resuppression.

Patients who remained non-suppressed and did not switch

Twenty eight (16%) patients (seven on PI-, 20 on NNRTI- and one on NRTI-based regimens) had neither switched nor resuppressed at most recent clinic visit, median 26·8 months [5·5-51·9] after VL rebound. Median follow up of these patients was 2·2 years [0·5-4·3] and 8 patients were followed up for less than 6 months. Of the 28, three (11%) patients made no changes to their regimen and three (11%) increased their dose of all drugs in line with growth. Thirteen (46%) were off-ART at the end of follow-up and the remaining nine (32%)

made other ART changes: eight within-class changes (for simplification and toxicity); and one patient had repeated treatment interruptions due to poor compliance.

Resistance testing

Resistance tests performed up to six months prior to the confirmatory (second) VL rebound measurement and censor date were available for 102/170 (60%) children: 68/89 (76%) of those who switched; 17/53 (32%) who resuppressed, and 17/28 (61%) who neither resuppressed nor switched. Overall, major PI, NNRTI, and NRTI mutations were found in zero (0%), 70 (69%), and 61 (60%) patients, respectively, who started a regimen containing that drug class and had a resistance test during follow-up. The most common mutations present were M184V (found in 49% (48/102) of patients and associated with resistance to the NRTIs lamivudine, emtricitabine and abacavir), K103N (23%; 23/102), Y181C (20%; 20/102), V106M (15%; 15/102) (all associated with resistance to NNRTIs), and thymidine analogue mutations (13%; 13/102). Of 68 children who switched following a resistance test, 61 (90%) had mutations detected. Eighteen patients did not switch therapy despite having resistance to drugs in their ART regimen. Of these, 5 (28%) went on to resuppress <400c/ml (whilst taking the following drugs: three nevirapine, one efavirenz, one lopinavir) and 13 (72%) neither switched nor resuppressed (seven nevirapine, four efavirenz, two lopinavir). Of patients who resuppressed, 12 (71%) had no resistance mutations detected; however, of patients who neither switched nor resuppressed only three (18%) had no resistance mutations. Table 3 shows the resistance mutation summary by regimen and outcome among children initiated on PI or NNRTI based regimens. Among patients who resuppressed without switch, no children on PIs had resistance to that drug class whereas 4/10 (40%) of children on NNRTIs had resistance mutations associated with that drug class.

DISCUSSION

In this national cohort of HIV-infected children in the UK/Ireland, we found that 19% (170/900) of children experienced virological failure, of whom half switch to second-line ART and one third resuppressed without switch. The proportion who resuppressed without switch was higher than expected although similar findings have been reported in adult studies[18-20]. Among those with a resistance test available, 71% (12/17) of patients who resuppressed without switch had no detectable resistance mutations compared with 10% (7/68) of patients who switched. This indicates both that patients who resuppressed were less likely to have resistance mutations, and that resistance testing guided the decision to switch patients to second line therapy. Whilst treatment non-adherence is not routinely reported to CHIPS, as well as being difficult to measure quantitatively, it is likely that this was identified following VL rebound and addressed with the child and their carers. Interestingly, almost a third of children who experienced VL rebound made some ART drug changes, not meeting the switch criteria, *prior to rebound*; this indicates that issues surrounding adherence or drug intolerance may have already arisen prior to virologic failure. A quarter of children who initiated on a NNRTI-based ART regimen resuppressed following VL rebound; an unexpected outcome given the low resistance barrier associated with this drug class. The proportion resuppressing without switch was markedly higher at 61% (19/31) among those on PI-based first-line regimen, reflective of its high resistance barrier. Time to switch to second-line therapy was also significantly later in children on PI-based regimens. Switch occurred more rapidly in children with higher viral load, lower CD4% and later calendar year at VL rebound. This observation is similar to that in the IeDEA cohort in Southern Africa where children with more progressive disease (based on higher viral load, CD4% <25 at switch, CD4% decline >1%/month) were more likely to switch, while those taking a PI-based regimen were less likely to switch[21], which also reflects WHO recommendations to not switch young children <3-years with VL rebound on PI-based regimens[5]. Reluctance to switch a child failing PI-based therapy without thorough assessment of adherence is reasonable

considering that viral escape is more likely due to poor adherence than resistance in this setting[22]. This is supported by the findings of the PENPACT-1 study that showed no PI-resistance emerging despite delayed switching[11]; in our study resistance to PIs was also rare.

Previous studies of children, primarily on NNRTI-based regimens, have shown similar rates of virological failure at 12 months, although some of these studies used different definitions of failure (single elevated viral load measurements)[21, 23, 24]. Among patients who switched to second-line therapy in our study, we found a median [IQR] time from VL rebound to switch of 4·9 months [1·7-13·4] which is comparable or slightly shorter than studies in resource limited settings[21, 25]. When changing the VL rebound threshold to two consecutive viral load measurements above 1,000c/ml and 5,000c/ml, not surprisingly we found a higher estimated proportion of patients switching to second line therapy while the probability of resuppression without switch decreased with higher VL thresholds. Presumably this is associated with anxiety felt by clinicians about higher viral loads and an increased risk of developing resistance mutations. Among patients who switched to second-line ART, an estimated 85% (95% CI [75-91]) remained continuously suppressed <400c/ml at 12 months and 73% (95% CI [62-82]) at 24 months after switch. These rates of suppression are comparable to recent reports from Thailand and Africa, where all patients initiated on a PI-based second line regimen[26-28]. Another study of paediatric response to second-line ART in South Africa showed significantly poorer VL suppression in children receiving NNRTI-based as opposed to PI-based second-line therapy[29]. Six months after regimen change, VL suppression was 80% in the PI-based vs 25% in the NNRTI-based second-line group, although the sample was relatively small (n=74). The long term outcomes on second line therapy by regimen were not assessed in our study and warrants further investigation.

There are some limitations to this study. First, CHIPS is a cohort study so there may be unmeasured underlying determinants influencing results. Second, we did not have

adherence data within the cohort so were unable to determine if adherence interventions accounted for resuppression in those who did not change ART. Third, our results in terms of rate of switch or resuppression are only applicable to settings with routine viral load monitoring and access to resistance testing, and to patients experiencing VL rebound following their initial first-line suppression. Fourth, there may be some resistance tests that we were unable to match to CHIPS patients; therefore the level of resistance may be under-estimated. There may also be some selection bias on the part of clinicians in their decision of which patients upon, and when, to conduct resistance tests; this may be influenced by factors such as latest viral load, current ART regimen and perceived adherence. Finally, some patients may have switched but we were unable to identify this using the data. For example, patients who changed one or two ART drugs across class without documented reason for change were not considered to have switched (there were two cases like this). Similarly, patients who switched prior to confirmed VL rebound were excluded; it is possible that patients may have switched to second-line following a very high single VL result, and therefore the rate of switch may be underestimated.

In conclusion, in our cohort half (89/170) of patients with VL rebound switched to second-line therapy and a third (53/170) resuppressed without switching ART. Of the remaining patients (28/170; 16%), half remained on a failing regimen and half interrupted therapy until the end of follow up. Reassuringly, switching to second-line therapy was faster in children on NNRTI-based regimens with lower barriers to resistance, as well as those more at clinical risk with lower CD4% and higher viral load. Switching to second-line therapy was also faster in later calendar years, as more classes of second-line drugs, as well as child friendly formulations became available. Switching was delayed in patients taking boosted PI-based regimens; indeed clinicians are more likely to use such regimens in children who are likelier to have adherence issues and greater risk of viral rebound. PI-based regimens are known to have a more forgiving nature and the majority (19/31; 61%) of patients who initiated on PI-based ART regimens resuppressed without switch. More notably, a quarter of children who initiated

on NNRTI-based ART regimens resuppressed after viral rebound. The possibility of resuppression should be considered prior to switching, ideally informed by resistance test results and a review of adherence and dosing status, to ensure an optimal second line therapy can be found.

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Authors contributions:

Tristan Childs, Trinh Duong, Ali Judd, Di Gibb and Intira Collins were responsible for the study concept and design. Tristan Childs carried out the statistical analyses. Tristan Childs, Delane Shingadia, Ruth Goodall, Ali Judd, Di Gibb and Intira Collins drafted the manuscript. Delane Shingadia, Katja Doerholt, Hermione Lyall, and Di Gibb collected the data. All co-authors participated in discussions about the design of the study, interpretation of the findings, and critically reviewed the manuscript.

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Figure 1. Flowchart showing eligibility of CHIPS patients for this analysis

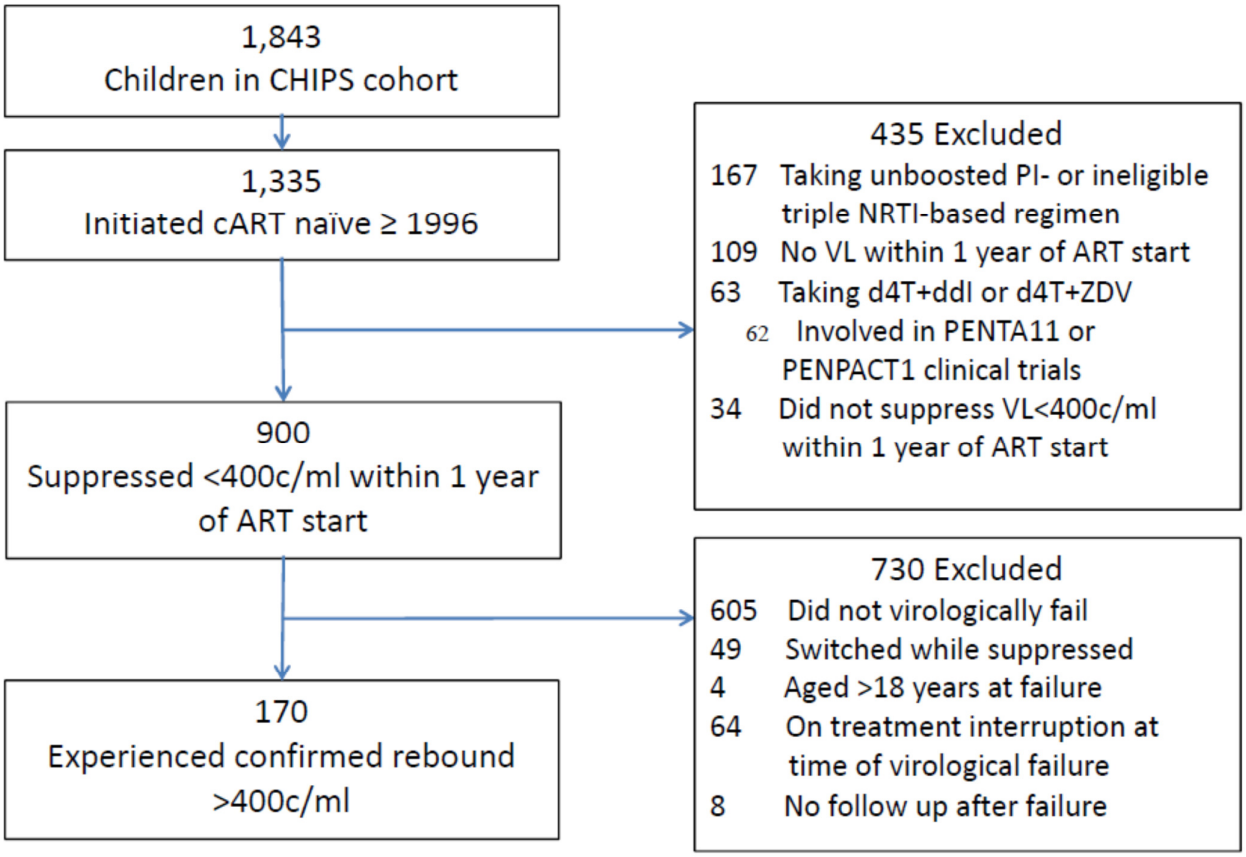

Table 1. Characteristics of patients who: suppressed within 12 months of initiating first-line ART; experienced viral load rebound after suppressing within 12 months of initiating first-line ART

	Suppressed within 12 months of initiating first-line ART		Experienced viral load rebound after suppressing within 12 months of initiating first-line ART	
Total number of patients	900		170	
Male	416	(46)	84	(49)
Age at ART initiation, median in years	7·9	[3·1-11·9]	7·5	[2·6-11·2]
< 3 years	222	(25)	44	(26)
CD4% at ART initiation , median	15	[9-20]	12	[6-17]
Calendar year at ART initiation				
1996-2003	270	(30)	86	(51)
2004-2007	328	(36)	53	(31)
2008-	302	(34)	31	(18)
Regimen at ART initiation				
Boosted PI+NRTI	171	(19)	31	(18)
EFV+2NRTI	373	(41)	53	(31)
NVP+2NRTI	199	(22)	51	(30)
NNRTI+3NRTI	113	(13)	23	(14)
3NRTI	44	(5)	12	(7)
Age at VL rebound, median in years			10·6	[5·6-13·4]
0-2			23	(14)
3-6			34	(20)
7-10			32	(19)
11-13			46	(27)
14+			35	(21)
CD4% at VL rebound			24	[17-32]
CD4 cell count at VL rebound, cells/µl			550	[310-930]
Viral load at VL rebound, $\log_{10}$ copies/ml			3·6	[3·1-4·2]
Time on ART until VL rebound, months			20·6	[9·7-40·5]
Calendar year at VL rebound				
1996-2003			38	(22)
2004-2007			58	(34)
2008-			74	(44)
Changes made to initial ART regimen prior to VL rebound				
None			119	(70)
Any			51	(30)
Cross class			10	(6)
Within class			8	(5)
NRTI backbone only			30	(18)
Other			3	(2)

ART, Antiretroviral therapy; EFV, Efavirenz; IQR, Interquartile range; NNRTI, Nonnucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor; NVP, Nevirapine; PI, Protease inhibitor; VL, Viral load.

Figure 2. Cumulative incidence of switch, confirmed resuppression without switch and neither resuppression nor switch following VL rebound, using competing risk model

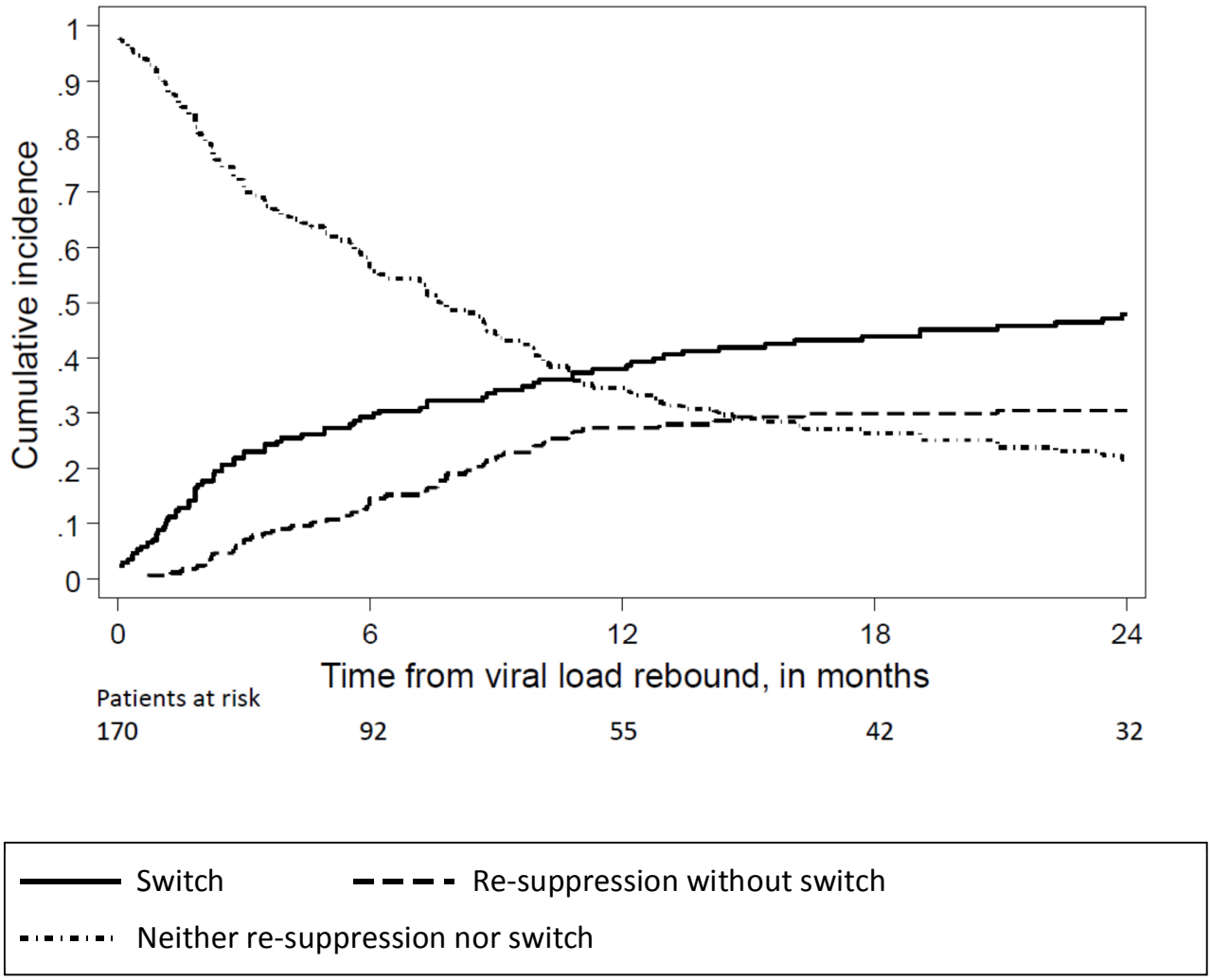

Table 2. Factors associated with time to switch following viral load rebound using competing risk model

		Univariable			Multivariable		
	n	SHR	95% CI	*P*	SHR	95% CI	*P*
Gender (female v male)	170	1·02	0·67 - 1·54	0·93			
Age at ART initiation (per 5 years higher)	170	1·05	0·85 - 1·28	0·67			
CD4% at ART initiation (per 5% higher)	145	0·85	0·75 - 0·97	0·02			
Age at VL rebound (per 5 years higher)	170	1·09	0·88 - 1·34	0·44	1·26	0·96 - 1·65	0·10
CD4% at VL rebound (per 5% higher)	160	0·90	0·80 - 1·00	0·04	0·89	0·78 - 1·01	0·07
Viral load at VL rebound (per $\log_{10}$ copies/ml higher)	170	1·72	1·29 - 2·27	0·0002	1·88	1·39 - 2·55	<0·0001
Time on ART until VL rebound (per 6 months higher)	170	1·02	0·96 - 1·09	0·44			
Regimen at ART initiation	170			0·01			0·001
EFV+2NRTI		1			1		
NVP+2NRTI		0·88	0·54 - 1·44		1·21	0·69 - 2·13	
Boosted PI+NRTI		0·18	0·07 - 0·48		0·13	0·05 - 0·38	
NNRTI+3NRTI		0·90	0·46 - 1·74		1·78	0·81 - 3·92	
ABC+2NRTI		0·76	0·40 - 1·43		1·45	0·73 - 2·91	
Calendar year at VL rebound	170			0·97			0·02
1996 - 2003		1			1		
2004 - 2007		1·06	0·65 - 1·74		1·28	0·71 - 2·30	
2008 - 2011		1·04	0·64 - 1·69		2·38	1·23 - 4·60	

ABC, Abacavir; ART, Antiretroviral therapy; CI, Confidence interval; EFV, Efavirenz; NNRTI, Nonnucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor; NVP, Nevirapine; PI, Protease inhibitor; SHR, Sub hazard ratio; VL, Viral load.

Table 3. Patient characteristics by initial ART regimen (PI or NNRTI) and outcome (switched or resuppressed)

	Initiated on PI-based regimen				Initiated on NNRTI-based regimen			
	Switched to second-line		Resuppressed without switch		Switched to second-line		Resuppressed without switch	
	N (%) or median [IQR]							
n	5	(100)	19	(100)	76	(100)	31	(100)
Male	3	(60)	10	(53)	36	(47)	15	(48)
Age at VL rebound, in years								
Median	12·6	[11·3,12·7]	13	[9·7,14·9]	10·7	[5·6,13·0]	5·3	[2·6,11·5]
<3	0	(0)	2	(11)	9	(12)	9	(29)
3-6	1	(20)	0	(0)	14	(18)	11	(36)
7-10	0	(0)	4	(21)	16	(21)	3	(10)
11-13	3	(60)	7	(37)	28	(37)	3	(10)
14+	1	(20)	6	(32)	9	(12)	5	(16)
VL at VL rebound (log10 copies/ml)	4	[3·9,5·1]	3·4	[2·9,3·7]	4	[3·5,4·4]	3·4	[3·0,4·0]
CD4 count at VL rebound (cells/µl)	422	[122,449]	420	[245,605]	550	[340,910]	922	[378,1246]
CD4% at VL rebound	7	[6,22]	22·5	[16,31]	24	[17,33]	27	[18,35]
Time from VL rebound to outcome, months	2·3	[1·7,19·1]	7·4	[3·0,9·9]	4·6	[1·4,12·2]	6·4	[3·2,10·1]
Calendar year at VL rebound								
1996-2003	1	(20)	0	(0)	14	(18)	9	(29)
2004-2007	1	(20)	4	(21)	30	(40)	13	(42)
2008-	3	(60)	15	(79)	32	(42)	9	(29)
Major resistance mutation(s) present (n=82)								
Number of patients with a resistance test	*4*		*7*		*61*		*10*	
PI/NNRTI	0	(0)	0	(0)	55	(90)	4	(40)
NRTI	2	(50)	1	(14)	43	(70)	2	(20)

ART, Antiretroviral therapy; EFV, Efavirenz; IQR, Interquartile range; NNRTI, Nonnucleoside reverse transcriptase inhibitor; NRTI, Nucleoside reverse transcriptase inhibitor; NVP, Nevirapine; PI, Protease inhibitor; VL, Viral load.