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What Should we do When HIV-Positive Children Fail First-Line Combination Antiretroviral Therapy? A Comparison of 4 ART Management Strategies

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Abstract

Background

Managing virologic failure (VF) in HIV-infected children is especially difficult in resource-limited settings, given limited availability of alternative drugs, concerns around adherence and the development of HIV resistance mutations. We aimed to evaluate four management strategies for children following their first episode of VF by comparing their immunologic and virologic outcomes.

Methods

We included children (aged <16 years) with VF from 8 IeDEA-SA cohorts, initiating cART between 2004-2010, who followed one of four management strategies: continuing on their failing regimen; switching to a second-line regimen; switching to a holding regimen (either lamivudine monotherapy or other non-cART regimen); discontinuing all ART. We compared the effect of management strategy on the 52-week change in CD4% and $\log_{10}$VL from VF, using inverse probability weighting of marginal structural linear models.

Results

982 patients were followed over 54168 weeks. Relative to remaining on a failing regimen, switching to second-line showed improved immunologic and virologic responses 52 weeks after VF with gains in CD4% of 1.5% (95% CI 0.2-2.8) and declines in $\log_{10}$VL of -1.4 copies/mL (95% CI -2.0, -0.8), whilst switching to holding regimens or discontinuing treatment had worse immunologic (-5.4% (95% CI -12.1, 1.3) and -5.6% (95% CI -15.4, 4.1)) and virologic outcomes (0.2 (95% CI -3.6, 4.1) and 0.8 (95% CI -0.6, 2.1) respectively.

Conclusions

The results provide useful guidance for managing children with VF. Consideration should be given to switching children failing first-line cART to second-line, given the improved virologic and immune responses when compared with other strategies.

Key Words: HIV, virologic failure, second-line, resource-limited settings, adherence

Introduction

By 2015 nearly 900 000 HIV-positive children were receiving combination antiretroviral therapy (cART),(1) most of whom are in sub-Saharan Africa. The shift to early cART initiation, results in HIV-infected children being on treatment for long durations, and virologic failure (VF) is a concern; an estimated 20% of children developing VF after 3 years of cART.(2) With limited alternative treatment options, and the difficulties of sustained adherence in this vulnerable group, managing VF in children in resource-limited settings (RLS) is particularly challenging. Adherence is especially difficult for children due to their dependence on caregivers for cART administration, difficulties facing families in disclosing HIV status to their child, the effects of HIV-associated stigma, and pharmaceutical challenges with pediatric drug formulations, dosing and drug-drug interactions.(3) Adolescents face their own adherence barriers, including the emotional challenges of puberty, and disclosing their HIV-status to others.(4)

Access to pediatric second- or third-line regimens is frequently restricted in RLS, where some newer drugs such as dolutegravir still require dosing studies and registration. Hence the optimal management of children with VF and suspected or proven poor adherence is challenging; switching to a new regimen risks increasing resistance mutations if adherence is not assured. Delays in switching patients from failing regimens are common, but have negative consequences.(2, 5) The South African national guidelines recommend careful assessment of adherence among children with VF before switching to second-line, and suggest "holding strategies" for those with ongoing adherence challenges.(6) "Holding regimens", such as lamivudine monotherapy (LM) may retain HIV variants with reduced viral fitness, particularly the M184V mutation, slowing immune decline whilst ensuring no new drug resistance develops.(7-9) Complete treatment interruption may also allow adherence barriers to be

addressed without new drug resistance emerging.(10) There is little evidence weighing the relative benefits and risks of these different strategies following VF in children. Fairlie et al. compared four management strategies following the most recent episode of VF, in an observational study from US-based pediatric cohorts,(11) but no comparative study has yet been done in RLS in sub-Saharan Africa, or following the first episode of VF.

Using causal inference methods and observational data from over 14,000 children in the International epidemiologic Database to Evaluate AIDS (IeDEA) Southern Africa, we compared immunologic and virologic outcomes after VF for those managed with the following strategies: switching to second-line cART, continuing on failing first-line cART, switching to non-cART holding regimens, and discontinuing all antiretrovirals.

Methods

We included data collected prospectively from eight IeDEA cohorts in South Africa. IeDEA is a multi-regional collaboration of HIV cohort studies.(12) Each study site had institutional ethical approval to contribute data to IeDEA analyses. Children (<16 years) initiating cART from 2004 to 2010, with documented VF after at least six months on cART were included. Final database closure was June 2012.

All study sites are part of the South African national ART program where virologic monitoring is routinely used. Table 1 provides details of the recommended first-line regimens during the study period.(13-15) The recommended second-line regimen prior to 2010 was to switch from an efavirenz-based to a lopinavir/ritonavir(LPV/r)-based regimen and switch at least one nucleoside reverse transcriptase inhibitor (NRTI). Prior to 2010, children failing protease-inhibitor (PI)-based first-line were switched to non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART. From 2010 guidelines recommended specialist referral for children failing PI-based

regimens as they require resistance testing and potentially integrase inhibitors, second generation PIs or NNRTIS such as darunavir and etravirine.(13)

We defined virologic failure (VF) as having at least two consecutive viral loads (VL) >1000 copies/ml, measured at least one month and less than one year apart. The date of VF was the date of the second unsuppressed VL. We considered only the first episode of VF.

We defined cART as comprising at least three antiretroviral drugs from at least two different drug classes. We compared four management strategies:

- Remaining on a failing first-line regimen, with at most one single drug substitution not constituting a drug class change.
- Switching to second-line: changing at least one drug including a change in drug class.
- Switching to a holding regimen: a regimen not meeting the definition of cART, such as one or more drugs from a single class, or only two drugs from two drug classes.
- Treatment interruption (TI): discontinuing all antiretroviral drugs.

The outcomes were the CD4% and $\log_{10}$VL slope, which were calculated at each time point after VF with a recorded CD4% or $\log_{10}$VL measure, as the difference between the current CD4%/ $\log_{10}$VL and the CD4%/ $\log_{10}$VL at VF, divided by the time in weeks between these two measurements. Patients were censored for death, transferring care or loss to follow-up (nine months without a recorded clinic visit prior to database closure).

Outcomes were modelled based on follow-up time on each strategy. Initially, we derived unweighted linear regression models for each outcome, adjusting for management strategy (allowing a four week lag to ensure the outcome reflected the appropriate strategy), covariates at VF, and weeks since failure. To estimate the effect of management strategy on the outcomes we adjusted for the time-dependent confounders VL and CD4%, which may have influenced both

clinician choice of management strategy and the respective outcome, using inverse probability of treatment weighting (IPTW) of marginal structural linear models.(16) To estimate the IPTW, we fitted a pooled multinomial logistic regression model for management strategy choice until a switch to second-line was made.(17) We used different model specifications, based on in/exclusion of variables, interaction terms, and the functional form of the variables. All models used stabilized weights as previously described.(17) We chose the final model based on Bayesian model averaging and the stability of the weights.(18) The final marginal structural model was a linear model with the slope of CD4% or $\log_{10}$VL (from VF to the current time point) as the outcome, weights to adjust for the confounding, and conditional on time and covariates at VF, including immune suppression, age, VL, being on a PI-based regimen and level of care. The stabilized weights had a mean of 1.008, minimum of 0.000924 and maximum of 12.2686.

Results

Across the eight sites, 1,347 (19%) of 7,053 children with recorded VL measurements on cART experienced VF, and 365 were excluded due to incomplete CD4% and regimen data. The final dataset comprised 982 children (46% female), with median age at VF of 6.1 years (IQR 2.7-10.7), and median duration on cART of 1.4 years (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D231). Median time between first and second consecutive VL >1000 was 90 days (IQR 66-140). Comparing patients based on their first change in management strategy, 557 (57%) remained on failing regimens throughout follow-up, 335 (34%) switched to second-line, 25 (3%) switched to holding regimens and 65 (7%) interrupted treatment. Most patients (95%) changed strategies only once. Among those switched to holding regimens, 80% were placed on NRTI-only regimens. Children switched to second-line were older, had lower

median CD4% at cART start, at failure and lower nadir CD4%. Few patients (32/398, 8%) on PI-based first-line were switched to NNRTI-based second-line.

At study closure, 9 (1%) patients had died (all having remained on their failing regimen), 216 (22%) transferred care, 90 (9%) were lost to follow-up (88 having remained on their failing regimen, 1 after switch to second-line and 1 after TI), and 667 (68%) remained in care at their original treatment site. Figure 1 shows management strategies at five points during the 52-week study period, 73% of follow-up time was spent on failing regimens, 24% on second-line, 1% on holding regimens, and 2% interrupting treatment. Median time to first change in strategy was 168 days (IQR 79-365), with median time from VF to second-line 115 days (IQR 62-203), to holding regimens 90 days (IQR 30-154), and to TI 123 days (IQR 52-259).

Choice of management strategy

Choice of management strategy was strongly associated with type of regimen at failure. Compared to those on PI-based first-line, those on NNRTI-based regimens were more likely to switch strategies than remain on failing first-line (Table 2). Those with the highest VL at VF (VL>50,000 copies/ml), were more likely to interrupt treatment (aHR 5.9, 95% CI 2.5, 13.8). Having a mid-range VL at VF (10,000-50,000 vs 1,000-5,000copies/ml) was associated with switching to a holding regimen (aHR 2.7, 95% CI 1.1, 7.0), indicating clinician preference to switch partially adherent patients to this strategy.

Outcomes: Change in CD4% and VL

Figure 2A and 2B shows the model estimates for the difference in mean 52-week change in CD4% and $\log_{10}$VL after VF, relative to remaining on a failing regimen and switching to second-line respectively. The final weighted model indicates that switching to second-line, even after operational delay, results in increases in CD4% and declines in VL compared to remaining on a

failing regimen. Switching to a holding regimen or interrupting treatment results in declines in CD4% and increases in VL, albeit with wide confidence intervals.

We conducted a separate analysis restricted to children on NNRTI-based first-line, for whom alternative regimens at the time were more robust than for those failing PI-based first-line (Figures 2C and 2D). Overall, the results were similar except the estimated declines in CD4% for those interrupting treatment compared to switching to second-line were significant and much larger than for all patients. When we compared switching to a holding regimen relative to TI we found that those interrupting treatment experienced bigger declines in CD4% (-12.1, 95% CI -29.1; 4.9). Due to small numbers switching to second-line NNRTI from a PI-based first-line, we were unable to conduct a restricted analysis for this group.

Estimates were stable in sensitivity analyses exploring alternative model specifications, with estimates for holding regimens or TI being more sensitive to model specifications given their smaller sample sizes (not published).

Discussion

This collaborative analysis of almost 1000 children with VF from eight South African cohorts showed that switching to second-line cART results in the best immunologic and virologic outcomes. The relative immunologic benefits and risks of using holding regimens was quantified; for patients with VF on NNRTI-based first-line, switching to a holding regimen may be better than TI, but has worse outcomes than remaining on failing first-line, while switching to LPV/r-based second-line cART, if available and where adherence is addressed, has the best outcomes.

To our knowledge, this is the first study comparing management strategies for children with VF from sub-Saharan Africa, where the burden of pediatric HIV is highest, and treatment options

most limited. This study also represents the best comparative data on the use of holding regimens. Our estimates are likely conservative and potentially underestimate the true effect size for two reasons: (i) we considered immunologic and virologic trajectories from "baseline" measurements taken at VF, however most patients first spent time on their failing regimen before switching strategies; (ii) we assumed patients were adherent to their assigned strategies, but misclassification of strategy may have occurred, with unrecorded TI being most likely. Since VL monitoring for patients on non-cART regimens is not routinely performed, our virologic results for holding regimens and TI have very wide confidence intervals. Apart from VL as a proxy measure, no adherence data was available. Adherence is likely a key consideration of management strategy choice and hence there may be unmeasured residual confounding. We had no data on drug resistance mutations, and could not assess its effect on immunologic and virologic trajectories. Remaining on failing NNRTI-based cART, runs a higher risk of accumulating drug resistance(19) compared to remaining on failing PI-based cART, where resistance is less likely unless there has been exposure to unboosted PI treatment.(20) Outcomes of remaining on failing regimens may therefore differ depending on regimen.

Our results are largely in agreement with Fairlie et al's study which was of similar design. They found switching to new cART had better immunologic outcomes compared to remaining on a failing regimen, with TI having the worst outcomes. Conclusions about their drug-sparing group could not be reached due to small numbers and large variety in the drug-sparing regimens used.(11) Clinician's decision-making of management strategy may not be comparable to our study, since treatment options, availability of resistance testing and resistance patterns were likely different for the mostly heavily treatment–experienced US-based study population.

Compared to TI, switching to a holding regimen resulted in smaller increases in VL, and for those on NNRTI-based first-line, much smaller immune decline. Whilst there are few comparative studies addressing holding regimens in children and adolescents, there is evidence in adults that LM has better immunologic and virologic outcomes than TI.(21) The IMPAACT P1094 study enrolled children failing non-NNRTI-based cART, and aimed to compare outcomes of those randomized to continue with failing non-NNRTI-based cART versus changing to either lamivudine or emtricitabine monotherapy. The study was discontinued due to lack of enrolment, but the available data indicates greater immune decline for those on holding regimens.(22) Descriptive studies of LM use found that most children experience substantial immune decline and some experience clinical deterioration, and recommend avoiding this strategy in those with low CD4 counts, and considering it only whilst awaiting second- or third-line drugs.(7, 23) Understanding the virologic and immunologic consequences of TI provides a useful benchmark for comparison. Planned TI is recommended in some countries for children to preserve future cART options, avoid long-term ART toxicity and because of difficulties in maintaining adherence.(24) Whilst this approach is severely detrimental in adults, outcomes are better among younger children or those with higher nadir CD4%.(25, 26) Unplanned TI, a consequence of poor or non-adherence to treatment, often occurs at a poorer clinical and immunological state, and increases the risk of AIDS-defining illness and hospitalization.(25) We could not determine the reason for TI in our study, but those interrupting treatment had the highest VL at VF, suggesting unplanned TI in those non-adherent. Several studies among children with planned TI, who were virally suppressed with high CD4, as well as those with unplanned TI, have documented rapid immune decline and virologic rebound in a similar range to our findings,(10, 25-28) although estimates have great inter-subject variability.

In conclusion, switching to second-line results in the best immunologic and virologic outcomes for children with VF. Where children are failing NNRTI-based cART and PI-based regimens are accessible, strong consideration should be given to early switch to second-line. Switching to holding regimens should be carefully considered, and reserved for use whilst awaiting access to suitable regimens. The most appropriate management strategy choice requires consideration of the available future treatment options and current adherence. Our findings inform that choice by quantifying the relative immunologic and virologic costs of delayed switching, holding regimens and TI in comparison to switching to second-line.

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Figure Legend:

Figure 1. Management Strategies followed from Virologic Failure during follow-up

Figure 2. Estimated change in CD4% and log viral load at 12 months after virologic failure from crude, unweighted and weighted generalized linear models

Table 1. Standard First-line Antiretroviral Therapy Regimens for HIV-infected Children in South Africa 2004-2012

	Before 2007	2007-2010	After 2010
Co-infected with tuberculosis	Stavudine, Lamivudine, Ritonavir	Stavudine, Lamivudine, LPV/r + Ritonavir	Abacavir, Lamivudine, LPV/r + Ritonavir
Less than 6 months old	Stavudine, Lamivudine, Ritonavir	Stavudine, Lamivudine LPV/r	Abacavir, Lamivudine, LPV/r
Less than 3 years old or less than 10 kg	Stavudine, Lamivudine, LPV/r	Stavudine, Lamivudine, LPV/r	Abacavir, Lamivudine, LPV/r
Older than 3 years old and more than 10kg	Stavudine, Lamivudine, Efavirenz	Stavudine, Lamivudine, Efavirenz	Abacavir, Lamivudine, Efavirenz

LPV/r: Lopinavir/ritonavir

Table 2. Associations with Management Strategy Choice in Children with Virologic Failure, Relative to Remaining on a Failing Regimen

	aHR (95% CI)*		
Characteristics at virologic failure	Switch to second-line	Switch to holding regimen	Treatment interruption
Type of first-line regimen (NNRTI-based vs PI-based)	8.86 (5.96-13.18)	3.18 (1.95-5.18)	1.87 (1.28-2.73)
Gender (female vs male)	0.81 (0.65-1.01)	0.83 (0.58-1.20)	1.13 (0.86-1.48)
Calendar year of ART start	1.06 (0.99-1.13)	1.32 (1.19-1.46)	1.10 (1.02-1.19)
Type of facility (primary vs secondary/tertiary)	2.97 (1.99-4.44)	2.73 (1.31-5.69)	22.78 (5.62-92.31)
Age in years at failure	1.07 (1.01-1.13)	0.95 (0.85-1.06)	1.20 (1.12-1.28)
Viral load at failure (copies/ml)			
1000-5000	1	1	1
5000-10000	1.73 (0.80-3.75)	1.25 (0.43-3.69)	3.18 (1.06-9.52)
10000-50000	1.63 (0.77-3.46)	2.72 (1.06-6.95)	5.72 (2.42-13.50)
>50000	1.45 (0.68-3.10)	0.44 (0.16-1.16)	5.93 (2.54-13.84)
Viral load at failure x Age in years at failure			
VL >1000 and VL<5000 x Age at failure	1	1	1
VL>=5000 and VL <10000 x Age at failure	0.95 (0.88-1.03)	0.99 (0.86-1.14)	0.76 (0.67-0.86)
VL>=10000 and VL <50000 x Age at failure	0.95 (0.88-1.02)	0.86 (0.75-0.99)	0.82 (0.75-0.89)
VL>=50000 x Age at failure	0.94 (0.87-1.01)	1.08 (0.95-1.22)	0.74 (0.68-0.82)
Time-varying covariates			
Current Log_{10}VL (per 1 Log_{10} increase)	1.58 (1.38-1.79)	2.33 (1.89-2.88)	2.18 (1.89-2.52)

*Hazard ratios derived from pooled unweighted multinomial logistic regression fit on subsample of person-weeks of follow-up during which a switch to new regimen had not yet occurred
aHR: adjusted hazard ratio

Figure 1

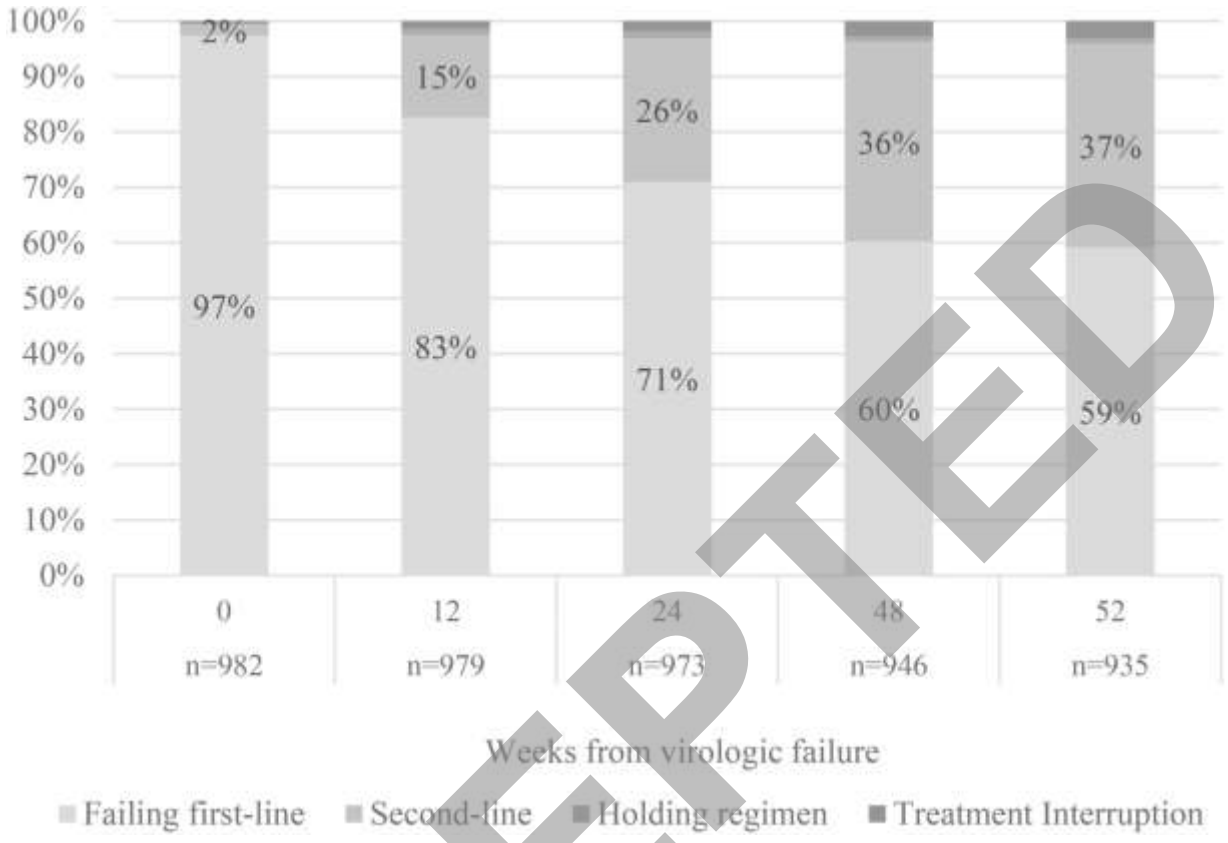

Figure 2