High virological failure rates in HIV-1 perinatally infected children in South Africa: A retrospective cohort study

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Background. Large cohorts of HIV-1 perinatally infected children with long-term follow-up in developing countries are limited.
Objectives. To explore rates and predictors of virological failure in a paediatric cohort.
Methods. A 10-year retrospective study was conducted from January 2004 to December 2013 to determine the incidence of and factors associated with virological failure among 1 659 HIV perinatally infected children in a public sector setting in South Africa (SA). Children aged <17 years who initiated first-line antiretroviral therapy between 1 January 2004 and 31 December 2013 and had at least 5 years of HIV viral load measurements were eligible.
Results. The 1 659 children contributed 7 075 person-years of follow-up (PYFU). In the initial cohort of 2 024 children, 51.0% were male and 62.0% were aged <5 years. The incidence of virological failure was 18.7 per 100 PYFU. Virological failure was associated with male gender, death of the mother, concurrent tuberculosis treatment and World Health Organization stage IV disease. Of the 320 HIV isolates successfully amplified, 249 (77.8%) had drug resistance mutations.
Conclusions. We observed high rates of virological failure and emergence of HIV drug resistance mutations. Despite gains made by SA in the treatment of HIV, such results challenge the country's ability to meet global targets of 90% viral suppression by 2020.

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The rapid scale-up of global HIV antiretroviral therapy (ART) in resource-limited settings has resulted in the successful enrolment of millions of HIV-infected children into care and treatment programmes.[1] South Africa (SA) has made great strides in HIV treatment, and has the largest ART programme in the world, with ~4.4 million people receiving ART.[2]

The scale-up of ART has resulted in improvements in virological and immunological parameters, as well as reductions in mortality, morbidity and comorbidities.[3,4] However, viral load rebound may still occur in some patients, despite an initial good response to ART. Maintenance of maximal and durable suppression of plasma viraemia has been particularly challenging for HIV-infected children, and non-adherence is often the strongest predictor of failure to achieve viral suppression.[5-7] The challenges that limit high adherence in children include complex ART regimens, significant side-effects, limited availability of paediatric formulations, the lifelong duration ART, and dependence on a caregiver to administer the medication.[8-10] A systematic review of resistance data in children from developing world settings found that 90% of those failing first-line regimens had at least one detectable resistance mutation.[11] Virological failure rates of up to 50% have been reported in African children during the 12 - 24 months after ART initiation.[12-14]

Studies that include long-term follow-up of children on combination ART (cART) are limited; it is therefore difficult to generate reliable estimates of the incidence of first-line failure in large paediatric cohorts in public sector settings and to identify the factors associated with virological failure. We therefore analysed data from a large cohort of HIV-positive children and adolescents receiving care in one of the largest public sector ART programmes in SA to estimate the cumulative incidence of virological failure, identify the determinants of virological failure, and evaluate the emergence of drug resistance.

Methods

Study population

A retrospective cohort study of HIV-1 perinatally infected children was conducted at the Dr George Mukhari Academic Hospital (DGMAH) in Pretoria, SA. Patients included in the study were aged <17 years, initiated first-line ART between 1 January 2004 and 31 December 2013, and had at least 5 years of HIV viral load measurements. Longitudinal clinical and demographic data were collected from the clinical files until last follow-up review or up to a 5-year time point following the initiation of ART. Failure to achieve an HIV viral load below the limit of detection was assessed at multiple time points during a 5-year period. For the purposes of this study, virological failure was defined as a viral load of >1 000 copies/mL 1 year after ART initiation.

HIV drug resistance

HIV genotyping was performed using an in-house drug resistance assay. Briefly, a 1.7 kb amplicon was generated by reverse transcriptase (RT)-initiated polymerase chain reaction of the entire protease (PR) and partial RT-coding regions. The amplicon was sequenced using five primers and included codons 1 - 99 of PR and codons

1 - 230 of RT. Sequencing was performed with either an ABI PRISM 3730 Genetic Analyzer or an ABI PRISM 3100-Avant Genetic Analyzer (Applied Biosystems, USA). To identify drug resistance mutations and predict drug susceptibility, the Stanford HIV Drug Resistance Database version 8.3 (Stanford University, USA) was utilised. Susceptibility to boosted lopinavir (LPV), atazanavir and darunavir was determined using the penalty score where, from the total score for each of the three protease inhibitors (PIs), five levels of inferred drug resistance were reported as susceptible, potential low-level resistance, low-level resistance, intermediate resistance and high-level resistance.

Statistical analysis

Descriptive statistics were used to summarise continuous variables and counts, while percentages were used for categorical variables. The Kaplan-Meier method was used to estimate virological failure at different time points. The incidence of virological failure was calculated in person-years of observation. Univariate and multivariate logistic regression analyses were used to examine the relationships of independent variables with the primary outcomes. All variables were included in the multivariate analysis model with logistic regression using the enter model, and multivariate odds ratios (ORs) and respective 95% confidence intervals (CIs) were obtained. Variables with a p-value <0.05 and an adjusted hazard ratio with a 95% CI on the final model of multivariate logistic regression were considered statistically significant predictors of virological failure. The Cox proportional hazards model was used to identify factors associated with virological failure. Statistical tests were based on a two-sided significance, and a p-value ≤0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.1 software (SAS Institute, USA).

Ethical considerations

Sefako Makgatho Health Sciences University approved collection of clinical and HIV drug resistance data (ref. no. SMUREC/M/30/2017:PG). To protect patient confidentiality, all records were anonymised and deidentified prior to analysis.

Results

Of 2 234 HIV-positive perinatally infected children initiated on ART from 2004 to 2013, 210 children with HIV monitoring data missing from medical files were excluded. An additional 365 children who had <5 HIV viral load measurements at the time of study recruitment were also excluded, yielding 1 659 records for analysis (Fig. 1).

Baseline characteristics

Of the initial cohort of 2 024 children, 1 033 (51.0%) were male and 1 255 (62.0%) were aged <5 years, with 300 (23.9%) being <1 year of age. Seventy-six percent of the children presented with World Health Organization (WHO) stage III/IV disease, with a median (interquartile range (IQR)) nadir CD4% of 13.3 (7.23 - 21) and a median (IQR) baseline HIV viral load of 5.3 (4.5 - 5.8) $\log_{10}$ copies/mL. The median (IQR) duration on cART for the entire study population was 5 (2 - 7) years. Baseline and clinical characteristics are summarised in Tables 1 and 2.

First-line regimen

Children who initiated ART from 2004 to 2010 were placed on stavudine + lamivudine (d4T + 3TC), while those who initiated ART after 2010 received an abacavir (ABC) + 3TC-based nucleoside reverse transcriptase inhibitor (NRTI) backbone. Over half of the children <3 years of age were initiated on LPV/ritonavir (LPV/r) + 2 NRTIs (51.8%; 488/941). Despite the SA guidelines being followed, 41.8% of the children (393/941) were initiated on an efavirenz (EFV)-based regimen. The remaining children were on nevirapine (NVP) (n=48; 5.1%) and ritonavir (RTV) (n=12; 1.27%). Of children ≥3 years of age, 797 (73.6%) initiated ART consisting of a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen – 763 (70.5%) on EFV and 9 (0.8%) on NVP.

An RTV-boosted PI (LPV/r) accounted for 38.7% (784/2 024) of the PI regimens prescribed. The proportion of patients on a PI regimen varied according to age categories: 62.2% (n=488) for those aged <3 years, 7.9% (n=62) for those aged 3 - 5 years, 21.7% (n=170) for those aged 6 - 10 years, and 8.2% (n=64) for those aged 11 - 16 years.

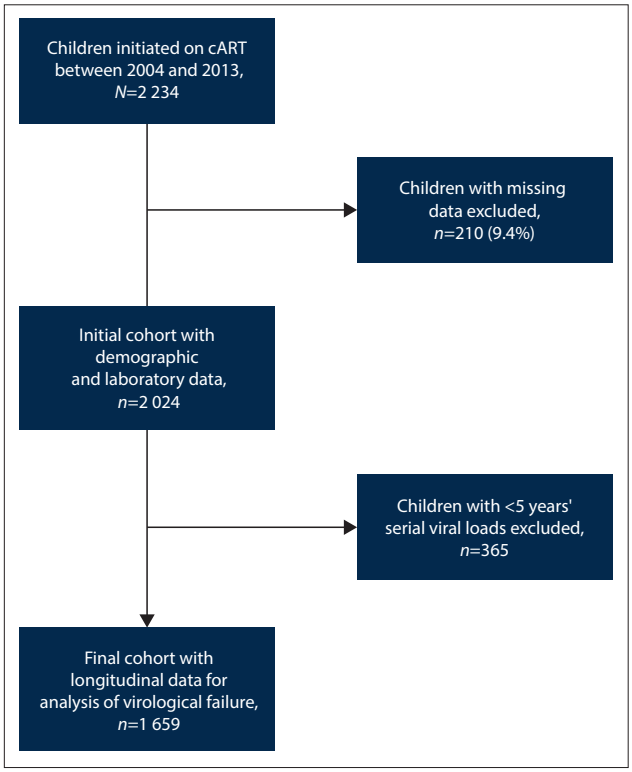

Fig. 1. Flow diagram of the medical files selected for virological failure analysis. (cART = combination antiretroviral therapy.)

Table 1. Baseline characteristics of the initial cohort of children (*N*=2 024)

Characteristic	*n* (%)
Gender	
Female	991 (49.0)
Male	1 033 (51.0)
Age (years)	
<1	300 (14.8)
1.1 - 5	955 (47.2)
5.1 - 10	576 (28.5)
10.1 - 15	190 (9.4)
15.1 - 17	3 (0.1)
Maternal status	
Alive	1 423 (70.3)
Deceased	601 (29.7)

Table 2. Clinical characteristics of the initial cohort of children (*N*=2 024)

Characteristic	*n* (%)
WHO stage	
I	142 (7.0)
II	310 (15.3)
III	1 149 (56.8)
IV	390 (19.3)
Unknown	33 (1.6)
CD4%	
0 - 9	455 (22.5)
10 - 15	395 (19.5)
16 - 20	284 (14.0)
>20	470 (23.2)
Unknown	420 (20.7)
ART regimen	
d4T, 3TC, EFV	548 (27.1)
d4T, 3TC, NVP	47 (2.3)
d4T, 3TC, LPV/r	211 (10.4)
d4T, 3TC, RTV	8 (0.4)
AZT, 3TC, EFV	140 (6.9)
AZT, 3TC, NVP	33 (1.6)
AZT, 3TC, LPV/r	88 (4.3)
AZT, 3TC, RTV	5 (0.2)
ABC, 3TC, EFV	465 (23.0)
ABC, 3TC, NVP	4 (0.2)
ABC, 3TC, LPV/r	472 (23.3)
ABC, 3TC, RTV	0
AZT, ddI, LPV/r	1 (0.04)
ABC, ddI, LPV/r	1 (0.04)
AZT, EFV, NVP	1 (0.04)
ART selection at initiation (<3 years of age)	
LPV/r	488 (24.1)
EFV	393 (19.4)
NVP	48 (2.4)
RTV	12 (0.6)
ART selection at initiation (≥3 years of age)	
EFV	778 (71.8)
LPV/r	296 (27.3)
NVP	9 (0.8)
RTV	0
Concurrent TB treatment	
Yes	619 (30.6)
No	1 405 (69.4)

WHO = World Health Organization; d4T = stavudine; 3TC = lamivudine; EFV = efavirenz; NVP = nevirapine; LPV/r = lopinavir/ritonavir; RTV = ritonavir; AZT = zidovudine; ddI = didanosine; ABC = abacavir; TB = tuberculosis.

Incidence of virological failure

A total of 1 659 children were observed for 7 075 PYFU; of these, 425 (25.6%) experienced virological failure by 1 year post ART initiation. The incidence of virological failure after first-line ART among the children tested was 18.5 per 100 PYFU. The rates of virological failure at different time periods are shown in Fig. 2.

Twenty-five children (5.9%) had persistent viraemia with no evidence of viral suppression at each successive year up to 5 years. Despite the observed virological failure pattern, high levels of viral suppression were achieved by a large proportion of children, with 74% of the cohort achieving viral suppression at the 12-month visit,

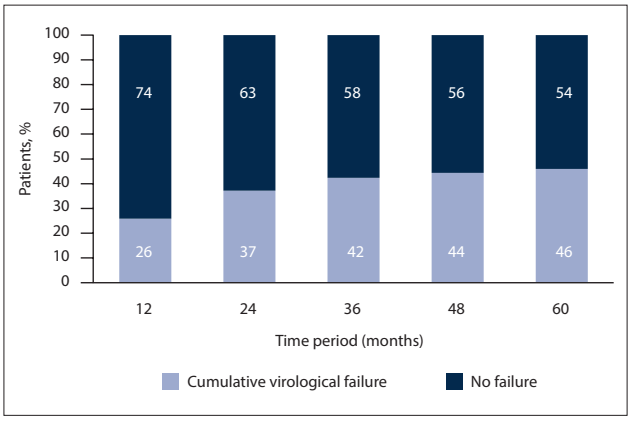

Fig. 2. Virological failure at different time periods.

1 378 (83%) at 2 years, 1 410 (85%) at 3 years, 1 475 (89%) at 4 years, and 1 485 (89%) at 5 years. The cumulative hazard of virological failure at 1 to 5 years post ART initiation was 12%, 20%, 27%, 32% and 36%, respectively.

Predictors of virological failure

Table 3 summarises univariate and multivariate risk factors associated with virological failure in HIV perinatally infected children. In univariate analysis, the nadir CD4% was the only variable statistically significantly associated with virological failure (p=0.042).

Male gender, age, concurrent tuberculosis (TB) treatment, and mother having died by the time the child presented, were independently associated with virological failure. Gender at 24 months post ART initiation was statistically significant, with increased odds of a male child having virological failure (OR 1.440, 95% CI 1.074 - 1.930; p<0.015). Additionally, concurrent TB treatment at ART initiation (p=0.0042), age (OR 1.066, 95% CI 1.026 - 1.109; p<0.001), and mother having died before ART initiation (OR 1.475, 95% CI 1.005 - 2.164; p<0.047) were found to be predictive of virological failure.

HIV drug resistance

Over the 5-year follow-up period, 337 children (20.3%) had plasma submitted for HIV resistance testing; of these samples, 17 failed to amplify. Of the remaining 320 samples, 71 (22.1%) displayed wild-type virus, while 249 (77.8%) had at least one drug resistance mutation. NNRTI resistance mutations were observed in 162/249 (65.1%), with 158/249 (63.4%) displaying dual-class NNRTI/NRTI resistance. The M184V mutation was present in 237 children (95.1%), and thymidine analogue mutations (TAMs) in 125 (43.8%). Among TAMs, the prevalence was 32% for D67N, 22.4% for K70R, 20% for K219Q/E/N, 32% for M41L, 14.4% for T215F/Y and 2.4% for L210W. The most common NNRTI mutations were K103N (n=92; 46.2%), V106M (n=61; 30.6%), Y181C (n=37; 18.6%), and G190A (n=37; 18.6%). Of the 94 children on a PI-based regimen at the time of genotyping (32.9%), 10.5% (30/285) harboured major protease mutations. Fifteen children displayed a K65R resistance mutation, with 7 records of children (46.6%) having no documented exposure to tenofovir.

Discussion

This study assessed virological failure in a large HIV paediatric cohort in a public sector setting in SA where routine viral load monitoring is available. Of HIV-infected children, 425 (26%) met the definition of virological failure at 1 year post ART initiation. Overall, the incidence rate of virological failure was 18.5 per 100 PFYU, and

Table 3. Logistic regression analysis of factors associated with virological failure (viral load >1 000 copies/mL)

	Year 1			Year 2			Year 3			Year 4			Year 5		
Characteristic	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Gender male	1.275	0.992 - 1.640	0.058	1.440	1.074 - 1.930	0.015	1.358	0.999 - 1.847	0.051	1.300	0.926 - 1.825	0.130	1.267	0.883 - 1.819	0.199
Age	0.986	0.960 - 1.013	0.319	1.000	0.969 - 1.032	0.992	0.996	0.964 - 1.029	0.802	1.020	0.984 - 1.057	0.286	1.066	1.026 - 1.109	0.001
Mother died	1.192	0.901 - 1.576	0.219	1.027	0.740 - 1.427	0.872	1.274	0.911 - 1.781	0.157	1.400	0.975 - 2.012	0.069	1.475	1.005 - 2.164	0.047
WHO stage			0.694			0.685			0.974			0.493			0.013
I	0.754	0.413 - 1.378	0.359	1.099	0.573 - 2.107	0.776	0.936	0.467 - 1.877	0.852	0.737	0.305 - 1.784	0.499	0.716	0.309 - 1.659	0.435
II	1.056	0.685 - 1.629	0.803	0.845	0.501 - 1.425	0.528	0.882	0.517 - 1.504	0.645	0.838	0.448 - 1.568	0.580	0.283	0.129 - 0.622	0.002
III	1.048	0.747 - 1.470	0.786	1.098	0.742 - 1.624	0.641	0.960	0.641 - 1.438	0.844	1.159	0.734 - 1.829	0.527	0.875	0.556 - 1.378	0.565
PTB	1.135	0.863 - 1.491	0.365	1.082	0.788 - 1.485	0.626	1.148	0.824 - 1.600	0.415	1.448	1.014 - 2.069	0.042	1.219	0.837 - 1.776	0.302
EPTB	0.000	0.000	0.999	1.555	0.170 - 14.215	0.696	1.858	0.203 - 17.035	0.584	2.333	0.251 - 21.701	0.457	0.000	0.000	0.999
PTBRx	2.942	0.182 - 47.588	0.447	4.168	0.257 - 67.658	0.315	5.200	0.320 - 84.547	0.247	0.000	0.000	0.999	0.000	0.000	0.999
CD4%	0.995	0.983 - 1.008	0.463	1.005	0.991 - 1.018	0.504	1.008	0.994 - 1.022	0.267	1.002	0.986 - 1.018	0.853	1.003	0.986 - 1.020	0.717

OR = odds ratio; CI = confidence interval; WHO = World Health Organization; PTB = pulmonary tuberculosis; EPTB = extrapulmonary tuberculosis; PTBRx = pulmonary TB treatment.

the 5-year cumulative incidence of failing on a first-line regimen was 36%. These findings are higher than virological failure rates of 6 - 16%[15-18] reported in other SA settings, although virological failure rates of 20%[19] and 26%[20] in Thai and Ugandan children, respectively, are consistent with our findings. With children reported to be at higher risk of virological failure than adults,[21] much higher rates have been reported in clinical programmes in Kenya, Mali and Cote d'Ivoire.[22-24] Of note, with different viral load cut-off points and varying follow-up periods in different studies, a direct comparison of virological failure rates is difficult. While a relatively high proportion of children with virological suppression on ART is reassuring, the current failure rates fall short of the goals of achieving 90% viral suppression by 2020 for those on ART.

Of particular concern are the 25 children (5.9%) with persistent viraemia at each successive year for up to 5 years. However, these figures are much lower than the reported persistent viraemia of 57% reported by Davies *et al.*[25] in a similar cohort. Clinicians' non-adherence to protocols for switching to second-line ART is a challenge that has been reported in the SA public setting, and such delays lead to the emergence of HIV drug resistance, compromising subsequent regimens.[26-29]

In the present study, children with a low nadir CD4%, male gender, concurrent TB treatment and maternal death were at increased risk of virological failure, highlighting a need to intensify adherence counselling in such population groups. The association of virological failure with low nadir CD4%, male gender, concurrent TB treatment and the death of a mother has been described previously.[30-38]

Our finding of a prevalence of HIV drug resistance of 78% corroborates reports of high proportions of children with emergence of HIV drug resistance mutations in SA.[13,16,39-41] The high prevalence of HIV drug resistance in our cohort was largely driven by resistance to NNRTIs, with 62% of children on EFV at the time of genotyping. Among NRTIs, the most prevalent HIV drug resistance mutations were M184V and TAMs, reflecting the extensive use of d4T or AZT and 3TC as part of the first-line regimen prior to the replacement of d4T with ABC. The proportion of wild-type virus (22.1%) was consistent with other studies reporting between 9%[15] and 22%,[40] highlighting non-adherence issues.

Study strengths and limitations

This study has several strengths, including the relatively large sample size and a high number of children initiated from 2004 to 2013. Paediatric resistance data were also drawn from an HIV clinic with real-time viral load monitoring. Nonetheless, the DGMAH clinic is a tertiary centre serving a semi-urban population and may not be representative of HIV public sector paediatric clinics across all of SA. Moreover, antiretroviral medications administered for the prevention of mother-to-child transmission were not consistently recorded in all the patient files. The impact of different antiretroviral agents on HIV transmission resistance and the development of drug resistance could therefore not be examined. Other limitations were the lack of documentation of adherence activity, use of traditional medications, and paediatric national ART guidelines influencing regimen changing over the study period.

Conclusions

Virological failure and emergence of HIV drug resistance remain major challenges for paediatric ART management in this SA healthcare setting.

Declaration. The research for this study was done in partial fulfilment of the requirements for ZNM's PhD (Virology) degree at the Sefako Makgatho Health Sciences University.

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Author contributions. ZNM contributed to the study concept, study design and data collection and wrote the manuscript. JTB, OT, SM and PM reviewed the manuscript and approved the final version for publication.

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Conflicts of interest. None.

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