Short-term treatment outcomes of children starting antiretroviral therapy in the intensive care unit, general medical wards and outpatient HIV clinics at Red Cross War Memorial Children's Hospital, Cape Town, South Africa: A retrospective cohort study

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Background. Many HIV-infected children are initiated on antiretroviral therapy (ART) during hospitalisation in South Africa (SA). No published data on these outcomes exist.
Objectives. To assess the short-term outcomes of children initiated on ART in the intensive care unit (ICU), general medical wards (GMWs) and outpatient HIV clinics (OHCs) at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, SA.
Methods. We conducted a retrospective cohort study of HIV-infected children aged <13 years commenced on first-line ART between January 2008 and December 2011. Outcomes included death, virological suppression and changes in CD4 count. Kaplan-Meier estimates, multivariate Cox proportional hazard ratios and logistic regression were used to estimate outcomes at 6 months.
Results. One hundred and six children were commenced on ART in the ICU, 509 in the GMWs and 127 in the OHCs; 65.7% of all children were <12 months old. Of children qualifying for rapid ART initiation according to the 2013 national treatment guidelines, 182 (24.9%) started therapy within 7 days of diagnosis. Overall mortality was 6.4% (95% confidence interval (CI) 4.9 - 8.4). Of children remaining in care at RCWMCH, 51.0% achieved a CD4 percentage ≥25% and 62.3% a viral load ≤50 copies/mL 6 months after ART initiation. Mortality was higher in the ICU cohort (13.2%) than in the GMW and OHC cohorts (5.5% and 3.9%, respectively, log-rank p=0.004). Predictors of mortality included moderate underweight (adjusted hazard ratio (aHR) 2.4; 95% CI 1.1 - 5.2), severe underweight (aHR 3.2; 95% CI 1.6 - 6.5), absence of caregiver counselling sessions (aHR 2.9; 95% CI 1.4 - 6.0) and ART initiation in the ICU (aHR 2.6; 95% CI 1.4 - 4.9).
Conclusion. These results highlight the importance of understanding the context in which children are initiated on ART, when comparing outcomes in different settings.

S Afr Med J 2015;105(3):220-227. DOI:10.7196/SAMJ.8950

The majority of HIV-infected children manifest clinical features of disease by 12 months of age.[1,2] A pooled analysis of HIV-infected children living in Africa showed that without optimal therapy 35.2% and 52.5% died by 12 and 24 months of age, respectively.[3] Conversely, the Children with HIV Early Antiretroviral Therapy (CHER) Study showed that if antiretroviral therapy (ART) was commenced during the first 3 months of life in asymptomatic HIV-infected infants with limited immunological suppression, mortality risk was reduced by 76% and disease progression by 75%.[4] Consequently, treatment programmes have progressively increased access to universal ART for infected children. In South Africa (SA), ART for all HIV-infected children aged <12 months was implemented in December 2009.[5] In March 2013, this policy was extended to all HIV-infected children aged <5 years, and expedited initiation of ART within 7 days of HIV diagnosis was recommended for all infants and older children with advanced clinical disease and/or severe immunosuppression.[6]

Although these policy changes encouraged increased access to ART, treatment coverage has remained relatively low in SA, resulting in high hospitalisation rates among HIV-infected children due to severe comorbidity. At the end of 2012, an estimated 63% of 220 000 children <15 years of age who required therapy were actually receiving ART in SA.[7] The majority of HIV-infected children requiring hospitalisation at Red Cross War Memorial Children's Hospital (RCWMCH), Cape Town, are ART-naïve infants, including many young infants. The median age of 1 360 children initiated on ART at RCWMCH during a 6-year period was 8 months, and 25% were ≤3 months of age.[8] Because the majority are infants with severe comorbidity, initiating ART during hospitalisation is a common clinical practice at RCWMCH.[9] With the advent of the 2013 national guidelines, it is likely that increasing numbers of young HIV-infected infants and children at other healthcare facilities across SA are being initiated on ART during hospitalisation. No published local studies have reported the outcomes of children initiated on ART during hospitalisation. To address this question, we examined the short-term outcomes of children initiated on ART in the intensive care unit (ICU), general medical wards (GMWs) and outpatient HIV clinics (OHCs) at RCWMCH.

Methods

Study location

This study was undertaken at RCWMCH, a tertiary referral hospital dedicated to the care of children up to 13 years of age. This includes

Table 1. Characteristics of HIV-infected children prior to ART initiation*

	Overall patient baseline characteristics	Patient characteristics stratified according to ART initiation location			
		OHCs	GMWs	ICU	*p*-value
Age (months), median (IQR)	*N*=749 5 (3 - 23)	*N*=127 22 (5 - 71)	*N*=509 5 (3 - 21)	*N*=106 3 (3 - 4)	0.0001
Age categories (months), *n* (%)	*N*=749	*N*=127	*N*=509	*N*=106	0.0001
<3	130 (17.4)	14 (11.0)	90 (17.7)	25 (23.6)	
3 - 12	362 (48.3)	37 (29.1)	247 (48.5)	72 (67.9)	
13 - 60	147 (19.6)	39 (30.7)	102 (20.047)	6 (5.7)	
>60	110 (14.7)	37 (29.1)	70 (13.8)	3 (2.8)	
Gender, *n* (%)	*N*=749	*N*=127	*N*=510	*N*=106	0.61
Female	379 (50.6)	60 (47.2)	258 (50.6)	57 (53.8)	
Male	370 (49.4)	67 (52.8)	252 (49.4)	49 (46.2)	
WAZ, median (IQR)	*N*=700 −2.14 (−3.42 - −0.95)	*N*=115 −1.14 (−2.47 - −0.23)	*N*=477 −2.33 (−3.56 - −1.17)	*N*=102 −2.48 (−3.91 - −1.37)	0.0001
WAZ categories, *n* (%)	*N*=700	*N*=115	*N*=477	*N*=102	0.0001
Mild-normal	331 (47.3)	82 (71.3)	210 (44.0)	47 (46.1)	
Moderate underweight	141 (20.1)	14 (12.2)	109 (22.9)	17 (16.7)	
Severe underweight	228 (32.6)	19 (16.5)	167 (35.0)	38 (37.3)	
HAZ, median (IQR)	*N*=525 −2.14 (−3.55 - −0.95)	*N*=121 −1.92 (−2.84 - −0.91)	*N*=338 −2.16 (−3.7 - −1.1)	*N*=61 −2.00 (−3.72 - −0.2)	0.20
HAZ categories, *n* (%)	*N*=525	*N*=121	*N*=338	*N*=61	0.02
Mild-normal	248 (47.2)	63 (52.1)	153 (45.8)	30 (49.2)	
Moderate stunting	110 (201.0)	34 (28.1)	64 (18.9)	10 (16.4)	
Severe stunting	167 (31.8)	24 (19.8)	120 (35.5)	21 (34.4)	
WHZ, median (IQR)	*N*=446 −1.2 (−2.61 - −0.04)	*N*=83 −0.04 (−1.29 - −0.8)	*N*=297 −1.53 (−2.8 - −0.3)	*N*=61 −1.37 (−2.82 - −0.31)	0.0001
WHZ categories, *n* (%)	*N*=446	*N*=81	*N*=297	*N*=61	0.0001
Mild-normal	293 (65.7)	72 (88.9)	180 (60.6)	37 (60.7)	
Moderate wasting	70 (15.7)	7 (8.6)	50 (16.8)	12 (19.7)	
Severe wasting	83 (18.6)	2 (2.5)	67 (22.6)	12 (19.7)	
CD4 percentage, median (IQR)	*N*=742 17.00 (10.0 - 24.6)	*N*=127 17.6 (10.4 - 24.4)	*N*=509 17.12 (10 - 25.3)	*N*=106 14.35 (8.9 - 22.5)	0.12
CD4 percentage, *n* (%)	*N*=742	*N*=127	*N*=509	*N*=106	0.27
≤25%	180 (24.3)	29 (22.8)	132 (25.9)	19 (17.9)	
>25%	562 (75.7)	98 (77.2)	377 (74.1)	87 (82.1)	
VL, *n* (%)	*N*=691	*N*=123	*N*=465	*N*=96	0.0001
≤100 000	183 (26.5)	58 (47.2)	109 (23.4)	15 (15.6)	
>100 000	508 (73.5)	65 (52.9)	356 (76.6)	81 (84.4)	
WHO stage, *n* (%)	*N*=741	*N*=127	*N*=502	*N*=106	0.0001
Stage 1	39 (5.3)	9 (7.1)	29 (5.8)	1 (1.0)	
Stage 2	62 (8.4)	19 (15.0)	40 (8.0)	3 (2.8)	
Stage 3	258 (34.8)	68 (53.5)	182 (36.3)	6 (5.7)	
Stage 4	382 (51.6)	31 (24.4)	251 (50.0)	96 (90.6)	
TB disease, *n* (%)	*N*=743	*N*=127	*N*=504	*N*=105	0.0001
None	558 (75.1)	82 (64.6)	380 (75.4)	89 (84.8)	
PTB	133 (17.9)	33 (26.0)	87 (17.3)	6 (5.7)	
EPTB	15 (2.0)	8 (6.3)	10 (1.98)	4 (3.8)	
PTB + EPTB	37 (5.0)	4 (3.1)	27 (5.4)	6 (5.7)	

Continued ...

Table 1. (continued) Characteristics of HIV-infected children prior to ART initiation*

	Overall patient baseline characteristics	Patient characteristics stratified according to ART initiation location			
		OHCs	GMWs	ICU	*p*-value
Time to ART initiation relative to TB rx initiation (days), median (IQR)	*N*=173 12 (24 - 1)	*N*=43 29 (92 - 16)	*N*=114 9 (16 - 2)	*N*=16 –6.5 (3 - –16)	0.0001
Time to ART initiation relative to HIV dx (days), median (IQR)	*N*=648 13 (7 - 38.5)	*N*=100 48 (26 - 250.5)	*N*=445 12 (7 - 28)	*N*=97 5 (3 - 9)	0.0001
Time to ART initiation relative to hospital admission (days), median (IQR)	*N*=749 7 (3 - 11)	*N*=127 NA	*N*=510 8 (6 - 13)	*N*=106 5 (3 - 7)	0.0001

IQR = interquartile range; PTB = pulmonary TB; rx = treatment; dx = diagnosis; NA = not applicable.
*In Table 1, non-normally distributed continuous variables were analysed using the Kruskal-Wallis non-parametric test. The χ^2 test of association and Fisher's exact test were used to test associations between categorical variables.

inpatient care, intensive care and outpatient follow-up for HIV-infected children.

Study design, inclusion criteria and baseline data collection

A retrospective cohort study was conducted. Children <13 years of age commenced on first-line ART between January 2008 and December 2011 at RCWMCH were included. Data were extracted from the ART Microsoft Access database. Additional baseline patient clinical information and maternal information were extracted retrospectively from hospital records. Data collected prior to starting ART included age, gender, CD4 percentage and absolute count, plasma HIV RNA concentration (viral load (VL)), growth status, World Health Organization (WHO) clinical stage, the presence of active tuberculosis (TB), and the time interval between HIV diagnosis and ART initiation. Ages were grouped into one of four categories: <3 months, 3 - 12 months, 13 - 60 months and >60 months. Mass and length/height measurements were transformed into weight-for-age *z*-scores (WAZ), height-for-age *z*-scores (HAZ) and weight-for-height *z*-scores (WHZ) using the WHO 2006 *Child Growth Standards*.[10] Moderate underweight, stunting and wasting were defined as WAZ, HAZ and WHZ between –2 and –3, and severe underweight, stunting and wasting as WAZ, HAZ and WHZ below –3. Primary baseline clinical conditions were defined as the disease process that probably contributed to hospital admission, as determined by the attending clinician. Extrapulmonary TB (EPTB) for the purpose of this analysis was defined as a patient with TB involving organs other than the lungs such as pleura, pericardium, lymph nodes, abdomen, joints and bones and meninges. Patients were stratified into one of three groups based on the site of ART initiation, i.e. ICU, GMWs or OHCs.

Counselling of caregivers by trained paediatric ART counsellors prior to ART initiation is usually practised at RCWMCH. The aim is to impart the knowledge and skills needed to provide treatment to their children. Three counselling sessions, each covering different aspects of the disease process, practical issues around treatment, and a formal demonstration in administering ART to affected children on an individualised basis, are provided before and during the course of ART initiation. These sessions are documented on a prescribed checklist.

Table 2. Characteristics of caregivers of HIV-infected children prior to ART initiation*

	Overall baseline caregiver characteristics	Caregiver characteristics stratified according to ARV initiation location			
		OHCs	GMWs	ICU	*p*-value
Reported maternal HIV status at ART initiation, *n* (%)	*N*=749	*N*=127	*N*=509	*N*=106	0.1
Positive	540 (72.1)	103 (81.1)	358 (70.3)	72 (67.9)	
Negative	46 (6.1)	4 (3.2)	32 (6.3)	10 (9.4)	
Unknown	163 (21.8)	20 (15.8)	119 (23.4)	24 (22.6)	
Maternal MTCT prophylaxis, *n* (%)	*N*=749	*N*=127	*N*=509	*N*=106	0.05
Yes	258 (34.5)	43 (33.9)	164 (32.2)	46 (43.4)	
No	353 (47.1)	68 (53.5)	243 (47.7)	40 (37.7)	
Unknown	138 (18.4)	16 (12.6)	102 (20.0)	20 (18.9)	
Maternal ART at ART initiation, *n* (%)	*N*=749	*N*=127	*N*=509	*N*=106	0.33
Yes	98 (13.1)	21 (16.5)	67 (13.2)	9 (8.5)	
No	487 (65.0)	85 (66.9)	325 (63.9)	70 (66.0)	
Unknown	118 (15.7)	10 (7.9)	94 (18.5)	15 (14.2)	
NA	46 (6.1)	11 (8.7)	23 (4.5)	12 (11.1)	
Primary caregiver status, *n* (%)	*N*=749	*N*=127	*N*=509	*N*=106	0.004
Mother	647 (86.4)	104 (81.9)	435 (85.8)	101 (95.3)	
Other	69 (9.2)	18 (14.2)	50 (9.9)	1 (0.9)	
None	33 (4.4)	5 (3.9)	24 (3.9)	4 (3.8)	

MTCT = mother-to-child transmission; NA = not applicable.
*In Table 2 the χ^2 test of association and Fisher's exact test were used to test associations between categorical variables.

Study outcomes

Outcome measures included death, loss to follow-up (LTFU), attrition, virological suppression and changes in CD4 count and percentage. Outcomes were evaluated at 6 months using the measure taken closest to 6 months after initiation, within a window of 3 - 9 months after ART initiation. LTFU was defined as failure to attend a follow-up visit within 3 months after the last scheduled appointment was missed. Attrition was defined as a combination of patients who had died and those who were LTFU during the study period.

Outcomes of those transferred out were determined using linkage with the Western Cape provincial laboratory database and

folder reviews. Mortality ascertainment was based on death documented in the RCWMCH folder, usually after re-presenting and being admitted to RCWMCH. Children who had specimen results of any nature recorded on the National Health Laboratory Service database at 6 months after ART initiation were considered alive. Children with no record of specimen results after transfer out and who were not documented to have died by 31 March 2013 were assumed to be LTFU.

Two cut-off values were used to define virological suppression, i.e. a VL of <400 copies/mL or <50 copies/mL. HIV RNA measurements were performed using Abbott Realtime HIV-1 assay and CD4 measurements by the PanLeucogated method.[11,12]

Statistical analysis

Pre-ART continuous variables were non-normally distributed and therefore compared using the Kruskal-Wallis test. Frequencies and proportions were used to describe pretreatment categorical variables. The χ^2 test of association or Fisher's exact test was used to assess associations between these variables. CD4 percentage and VL results at 6 months were compared with the respective baseline results using the Wilcoxon signed-rank test for paired samples. Kaplan-Meier curves were fitted to estimate mortality, LTFU and attrition probabilities during the first 6 months of ART.

Multivariable Cox proportional hazards regression was used to assess factors associated with mortality, LTFU and attrition during the first 6 months of ART, adjusting for pretreatment clinical and demographic variables. Logistic regression was used to assess factors associated with an unsuppressed VL during the first 6 months of ART, i.e. plasma HIV RNA concentration >400 copies/mL or >50 copies/mL, adjusting for pretreatment clinical and demographic variables. Variables with *p*-values of <0.1 on univariate analysis were included in the regression models.

The data were analysed using the STATA Release 12.0 statistical software package (STATACorp, College Station, USA).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town (reference number: HREC REF: 261/2002).

Results

In total, 878 children were treated with ART at RCWMCH during the study period. Of these, 129 were excluded from the analysis: 101 were ART experienced, and 28 had been initiated on ART at other healthcare facilities. Data from the remaining 749 children who fulfilled the inclusion criteria were analysed.

Baseline characteristics

Tables 1 and 2 describe patient and caregiver characteristics prior to ART initiation. One hundred and six children (14.5%) were commenced on ART in the ICU, 509 (68.0%) in the GMWs and 127 (17.0%) in the OHCs. Seven hundred and thirty-two children (97.7%) would have qualified for expedited initiation of ART according to the 2013 South African national treatment guidelines (492 were aged <12 months, 129 were aged >12 months with CD4 percentages <15%, and 111 were aged >12 months with WHO stage 4 disease). Of these children, 182 (24.9%) were initiated on treatment expeditiously, within 7 days of diagnosis. However, 367 (50.1%) were initiated within 7 days of hospital admission and a further 198 (27.0%) within 14 days. Children commenced on ART in the OHCs were significantly older than those in the ICU and GMWs. Overall, 65.7% of all children initiated on ART were <12 months old. Children in the ICU and GMW cohorts had significantly lower median WAZ scores and more wasting. More than 75% of children had subnormal CD4 percentages of <25%, and 385 (51.4%) had CD4 percentages <15% and/or CD4 counts <200 cells/μL. More children in the ICU and GMW cohorts than in the OHC cohort

Table 3. Primary diagnoses of children on presentation to hospital

	ICU (*N*=106)	GMWs (*N*=509)
Pneumonia	96	229
Gastroenteritis	5	137
Malnutrition	1	33
Septicaemia	1	14
PTB	-	13
EPTB	1	19
Upper airway obstruction	-	17
Meningitis	1	11
Non-accidental injury	-	4
Surgical conditions	1	9
Other medical conditions	-	23

PTB = pulmonary tuberculosis.

Table 4. CD4 percentage and VL responses after 6 months of ART

	GMWs	OHCs	ICU	*p*-value
CD4 percentage at 6 months, *n* (%)	*N*=330	*N*=99	*N*=59	0.1
≥25	158 (47.9)	55 (55.6)	36 (61.0)	
<25	172 (52.1)	44 (44.4)	23 (39.0)	
CD4% change at 6 months, median % difference (IQR)	*N*=320 4.7 (0.7 - 11.3)	*N*=91 3.2 (0.1 - 9.2)	*N*=54 9.1 (4.9 - 14.7)	0.001
VL (copies/mL) at 6 months, *n* (%)	*N*=280	*N*=93	*N*=51	
≤50	171 (61.1)	69 (74.2)	24 (47.1)	0.004
≤400	198 (70.7)	75 (80.7)	32 (62.8)	0.05
Log_{10} VL change at 6 months,* median % difference (IQR)	N=216 −4.7 (−2.9 - −5.9)	N=90 −4.7 (−3.8 - −5.4)	N=39 −4.1 (−1.5 - −5.3)	0.35

IQR = interquartile range.
*Analyses of the differences between 6-month and baseline CD4% or log_{10} VL values in children with paired specimen results.

had a baseline VL >100 000 copies/mL. Younger children, particularly infants, presented with higher VLs. The median VL $\log_{10}$ value of children aged <12 months was 6.0, while the median value for those aged >60 months was 4.8 (p=0.001). Overall a quarter of the children (24.7%) had current TB; of these, 6.5% had culture-confirmed disease and 19.2% probable TB. The times from HIV diagnosis and hospital admission to ART initiation were significantly shorter in the ICU cohort. No obvious differences were noted in caregiver characteristics prior to ART initiation. Most of the caregivers (92.9%) had at least one counselling session at RCWMCH, 53 (7.1%) receiving none. Not receiving counselling sessions was due to lack of caregiver availability during ART initiation (61.4%), patients being transferred out to other healthcare facilities before counselling sessions could be initiated (10.3%), or counselling taking place during follow-up visits after discharge from hospital (17.2%); in 11.1% of cases there was no documentation of reasons why counselling sessions were not performed. Pneumonia was the predominant primary diagnosis, present in 90.6% and 45.0% of children initiated on ART in the ICU and GMWs, respectively (Table 3).

Outcomes at 6 months

The Kaplan-Meier probability of overall mortality after 6 months of ART was 6.4% (95% confidence interval (CI) 4.9 - 8.4). Mortality at 6 months was significantly higher in the ICU cohort than in the GMW and OHC cohorts (Fig. 1, A). Among those who died, the median time to death after ART initiation was 25 days. Of the deaths in the GMW and ICU cohorts, 38 (90.5%) occurred during the primary hospital admission. Six children (3.1%) from the GMW cohort, 4 (3.2%) from the OHC cohort and 4 (2.4%) from the ICU cohort were LTFU by 6 months after starting ART. No statistical differences were found in the probabilities of LTFU (log-rank p=0.78) or attrition (log-rank p=0.12) between the three groups (Fig. 1, B).

After 6 months of ART, 51.0% of children remaining in care at RCWMCH had achieved a CD4 percentage of ≥25% and 62.3% a VL of ≤50 copies/mL. Paired analyses documented a significantly greater increase in median CD4 percentage over the first 6 months of ART among children initiated on ART in the ICU, with substantial declines in the median $\log_{10}$ VL values across all three treatment cohorts. The proportion of children achieving virological suppression was significantly lower in the ICU cohort (Table 4).

Of the 749 patients analysed, 257 were transferred out to primary healthcare facilities for continuation of care within 6 months of ART initiation. Where possible, CD4 and VL results after transfer out were obtained from the Western Cape provincial laboratory database. Of those transferred out, 142 (55.3%) had CD4 count results and 109 (42.4%) had VL results available 6 months after ART initiation. Paired analyses showed no significant differences in CD4 or VL log values at 6 months in children who were transferred out compared with those who remained in care at RCWMCH. Median increases in CD4 percentage at 6 months in those transferred out and those remaining in care were 4.0 and 5.8, respectively (p=0.165). Similarly, median decreases in VL log values at 6 months were 4.4 and 4.6, respectively (p=0.33), and there were no significant differences in the proportions of children achieving virological suppression. Of patients who were transferred out, 10 (3.9%) were LTFU and 9 (3.5%) died.

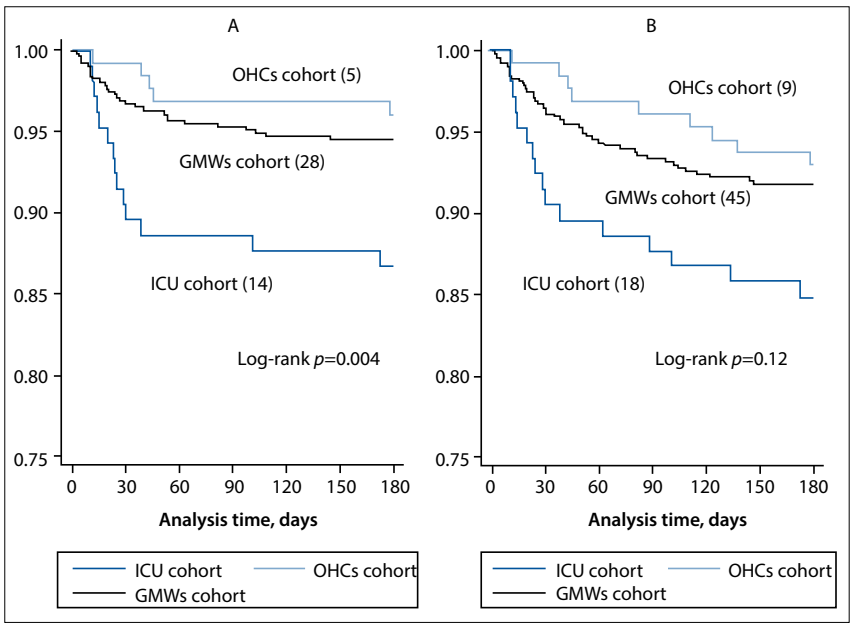

Fig. 1. Kaplan-Meier estimates for outcomes of (A) mortality (n=742) and (B) attrition (n=742) at 6 months, according to ART initiation location.

Predictors of mortality, attrition and an unsuppressed VL

On multivariable analysis, factors influencing mortality (Table 5) included age <3 months (adjusted hazard ratio (aHR) 1.8; 95% CI 0.9 - 3.4), moderate and severe malnutrition (aHR 2.4; 95% CI 1.1 - 5.2 and aHR 3.2; 95% CI 1.6 - 6.5, respectively), no caregiver counselling sessions before and during ART initiation (aHR 2.9; 95% CI 1.4 - 6.0), and starting ART in the ICU (aHR 2.6; 95% CI 1.4 - 4.9). Children with caregivers who were not on ART at baseline had a decreased hazard of death (aHR 0.5; 95% CI 0.3 - 0.9).

Regression modelling of those children who were LTFU within 6 months of ART initiation revealed that age was the only variable associated with LTFU; children between the ages of 3 and 12 months had a 3.16 increased risk of LTFU (p=0.02) compared with older children.

Factors influencing attrition included patient age, WAZ scores, number of caregiver counselling sessions, and caregivers who were on ART at baseline. Older children aged between 13 and 60 months had a decreased hazard of attrition (aHR 0.5; 95% CI 0.2 - 1.1). Children who were severely malnourished and children who had caregivers who did not receive any counselling sessions were at increased risk of attrition (aHR 1.8; 95% CI 1.1 - 2.8 and aHR 2.6; 95% CI 1.4 - 5.0, respectively).

Age was a major predictor of an unsuppressed VL (Table 6). Younger children were significantly less likely to achieve an undetectable VL. After 6 months on ART, 35.8% of children <12 months of age and 15.9% of those aged >12 months at the time of starting ART did not achieve a VL of <400 copies/mL. Furthermore, children <3 months of age had a 3.1-fold increased risk of a VL of >50 copies/ml (95% CI 1.8 - 5.3), while children between 3 and 12 months of age had a 2.6-fold increased risk of a VL of >50 copies/ml (95% CI 1.3 - 4.9) after adjusting for other predictors of virological response. Similarly, children <3 months of age had a 3.0-fold increased risk of a VL of >400 copies/ml (95% CI 1.5 - 5.9), while children 3 - 12 months of age had a 2.6-fold

Table 5. Predictors of mortality during the first 6 months of ART

	Univariate HR (95% CI) of mortality	*p*-value	Adjusted HR (95% CI) of mortality (*N*=700)	*p*-value
Age at ART initiation (months) (*N*=749)				
<3	1.8 (0.95 - 3.4)	0.07	1.8 (0.9 - 3.4)	0.07
3 - 12	1.2 (0.7 - 2.1)	0.59	1	
13 - 60	0.5 (0.2 - 1.2)	0.12	1	
>60	1		1	
WAZ categories (*N*=700)				
Mild-normal	1		1	
Moderate malnutrition	2.3 (1.1 - 4.8)	0.02	2.4 (1.1 - 5.2)	0.02
Severe malnutrition	2.5 (1.3 - 4.9)	0.008	3.2 (1.6 - 6.5)	0.001
Caregiver counselling sessions, *n** (*N*=749)				
0	3.8 (1.9 - 7.6)	0.0001	2.9 (1.4 - 6.0)	0.005
1	2.7 (0.7 - 11.1)	0.17	1	
2	0.6 (0.1 - 4.1)	0.58	1	
3	1		1	
ART initiation location (*N*=742)				
GMW	0.7 (0.4 - 1.2)	0.144	1	
OHC	1		1	
ICU	2.6 (1.4 - 4.9)	0.002	2.6 (1.4 - 4.9)	0.003
Caregiver support† (*N*=749)				
Yes	1		1	
No	1.0 (0.6 - 1.8)	0.95	1	
Not available	2.5 (1.2 - 5.2)	0.013	2.4 (1.1 - 5.0)	0.02
Maternal ART at ART initiation (*N*=749)				
Yes	1.1 (0.5 - 2.5)	0.762	1	
No	0.5 (0.3 - – 0.8)	0.011	0.5 (0.3 - 0.9)	0.02
Not available	2.3 (1.3 - 4.3)	0.005	1	
NA	1		1	

HR = hazard ratio; NA = not applicable.
*Number of counselling sessions received by caregiver prior to or during ART initiation.
†Is there a second caregiver who is able to administer ART to the child in the event of the primary caregiver not being present?

increased risk of a VL of >400 copies/ml (95% CI 1.4 - 4.6).

Discussion

Our study shows that ART-naïve HIV-infected children are still very much at risk of HIV-related morbidity and mortality, particularly those who are <3 months old. The majority of children initiating ART at RCWMCH were <12 months old; 85.4% had WHO stage 3 or 4 disease and 75.7% were immunocompromised (CD4 percentage <25%) at presentation to hospital. These findings are consistent with a previous analysis of infants <3 months old being initiated on ART across 20 clinics in Cape Town and Soweto, Johannesburg, SA. Advanced HIV disease was present in 62% of infants, suggesting that even earlier initiation of ART is required to prevent morbidity and mortality in young children.[13] Nevertheless, our study demonstrates that it was feasible to initiate ART rapidly after admission even in sick children, with mortality of 6.4% overall and <15% even in the sickest children who started ART in the ICU. In addition, LTFU was <5% among all groups of children. While most children experienced immune recovery, the low proportion with virological suppression by 6 months after starting ART, especially among infants, is a concern.

Only 24.9% of all children who fulfilled the 2013 SA national treatment criteria for expedited initiation commenced ART within 7 days of diagnosis. This figure is low because ART initiation in our cohort preceded the 2013 recommendations. Diagnosis of 152 study children prior to hospitalisation at RCWMCH also contributed to delayed initiation. The proportions of children initiated on ART within 7 and 14 days of hospitalisation were 49.0% and 75.4%, respectively, suggesting that not all hospitalised children who meet the criteria for expedited ART initiation will be commenced on ART within 7 days of HIV diagnosis.

A VL of <400 copies/mL was not achieved within 6 months of ART initiation in 35.8% of children aged <12 months and 15.9% of children aged >12 months, which is consistent with previous studies. Poor response in young children was described in a Soweto clinic, where the cumulative probability of achieving virological suppression (<400 copies/mL) 6 months after ART initiation was 59.4%. Children aged >36 months were more likely to achieve suppression at an earlier stage.[14] Failure to achieve virological suppression in young children may be attributed to several factors, including unpalatability of paediatric drug formulations, high baseline VLs in HIV-infected infants requiring a longer period to suppress, and choice of first-line ART regimens.

Before the roll-out of ART in the public sector, a sizeable proportion of HIV-infected children required admission to ICU facilities. Mortality in these children was high, with rates of 27% and 44% recorded at RCWMCH and Tygerberg Hospital, respectively.[15] Since the introduction of ART, mortality in children has decreased substantially. Our study reports a 13.2% probability of mortality in children admitted to the ICU and subsequently commenced on ART, which although significantly higher than those in the GMW and OHC cohorts, is approximately half the pre-ART ICU mortality. This reduction could be due to a combination of factors, including increased early HIV diagnosis and ART initiation in the ICU. Children requiring ICU care are more ill on presentation to hospital, which probably influences clinical, immunological and virological outcomes and possibly explains the increased mortality rate compared with the GMWs and OHCs. However, our results suggest that ART may have played a role in lowering ICU mortality. Other factors

Table 6. Predictors of an unsuppressed VL after 6 months of ART

	Univariate OR (95% CI)	*p*-value	Adjusted OR (95% CI) (*N*=338)	*p*-value
Predictors of VL >50 copies/mL				
Age at ART initiation (months) (*N*=429)				
<3	1.6 (0.95 - 2.7)	0.078	3.1 (1.8 - 5.3)	0.001
3 - 12	2.4 (1.6 - 3.5)	0.001	2.6 (1.3 - 4.9)	0.005
13 - 60	0.6 (0.4 - 0.9)	0.029	1	
>60	1		1	
Caregiver support* (*N*=429)				
Yes	1		1	
No	0.6 (0.4 - 0.97)	0.039	0.5 (0.3 - 0.9)	0.013
Not available	0.7 (0.3 - 1.4)	0.298	1	
Maternal ART at ART initiation (*N*=429)				
Yes	0.8 (0.5 - 1.4)	0.433	1	
No	1.7 (1.1 - 2.7)	0.012	1	
Not available	0.4 (0.2 - 0.8)	0.009	0.4 (0.2 - 0.8)	0.011
NA	1		1	
Predictors of VL >400 copies/mL				
Age at ART initiation (months) (*N*=429)				
<3	1.9 (1.1 - 3.3)	0.018	2.95 (1.5 - 5.9)	0.002
3 - 12	1.7 (1.1 - 2.7)	0.01	2.6 (1.4 - 4.6)	0.002
13 - 60	0.6 (0.4 - 1.1)	0.12	1	
>60	1		1	
Caregiver support* (*N*=429)				
Yes	1		1	
No	0.6 (0.4 - 0.97)	0.039	0.5 (0.3 - 0.9)	0.017
Not available	1.0 (0.5 - 2.3)	0.871	1	
Reported maternal HIV status at ART initiation (*N*=429)				
Negative	1		1	
Positive	1.8 (1.1 - 3.1)	0.024	1	
Not available	0.4 (0.2 - 0.7)	0.005	0.3 (0.1 - 0.6)	0.002

OR = odds ratio; NA = not applicable.
*Is there a second caregiver who is able to administer ART to the child in the event of the primary caregiver not being present?

possibly leading to improved outcomes, but not assessed in our study, include increased awareness and experience in managing ill HIV-infected children, as well as improved treatment practices. A quarter of children presenting to RCWMCH were diagnosed with TB either before or during presentation to hospital. The majority were commenced on anti-TB treatment before ART initiation, consistent with WHO and national guidelines

Psychosocial factors contribute substantially to successful outcomes of ART, in particular counselling of caregivers before and during ART initiation. Our study demonstrates a greater than two-fold increased risk of both mortality and attrition in the absence of caregiver counselling sessions. As most deaths occurred early during hospitalisation, absence of counselling is unlikely to have a causal effect on mortality. Indeed, caregiver unavailability was the major reason for caregivers not receiving counselling during ART initiation, reflecting the probable rapidity of ART initiation in these patients and the challenge of providing counselling when expediting ART.

Study strengths and limitations

A strength of this study lies in its novel contribution to the existing literature by examining the impact of ART initiation at different levels of healthcare in a tertiary hospital setting. It also provides an accurate reflection of healthcare function at an operational level in an overburdened healthcare system with a high turnover of patients.

Because this was a retrospective analysis, limitations in availability of routine data existed. Owing to a high transfer-out rate of children to other healthcare facilities after ART initiation, access to follow-up clinical and laboratory data proved challenging. In particular, missing outcomes data impeded our ability to reflect accurately on growth patterns, immunological reconstitution and virological suppression in the original cohort of children initiated on therapy. In general, children who are transferred out are less ill than those remaining in care. Virological and immunological outcomes of the entire cohort initially started on ART could in fact have been better than reported, had complete follow-up data on those transferred out been available. The results of this study are not generalisable to the

entire HIV-infected paediatric population, as our cohort was a select group, admitted to a tertiary healthcare centre and having severe disease. Also, the study was restricted to children starting ART as this was its primary focus; this limits our ability to assess the feasibility of commencing ART in all severely ill children, some of whom may have died before treatment could be initiated.

Conclusion

These results highlight the importance of understanding the context in which children start ART when comparing outcomes in different settings, and demonstrate feasibility and good mortality outcomes in very ill young HIV-infected children. Similar studies at other tertiary hospitals should be performed in order to corroborate our findings and provide a basis for developing and optimising consensus guidelines for managing severely ill HIV-infected children.

Funding. MAD receives funding from the National Institutes of Allergy and Infectious Diseases (Grant 2U01AI069924) for the International Epidemiologic Databases to Evaluate AIDS Southern Africa Collaboration.

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Accepted 20 October 2014.