From pediatric to adolescent HIV: mortality, viral suppression and transition to adult care

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Abstract

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Introduction: Global scale-up of prevention of mother to child transmission (PMTCT) programs and expansion of pediatric HIV testing and treatment have dramatically changed the course of pediatric HIV. Fewer infants are born with HIV, and early treatment significantly improves survival, growth, neurodevelopment and prevents morbidity. However, challenges with early diagnosis and achieving treatment goals during adolescence exist. A majority of HIV infected children present for care while severely ill, and experience high morbidity and mortality despite initiation of treatment. For children surviving to adolescence, maintaining viral suppression remains challenging, and mortality during adolescence is high. As children grow into adulthood, how to support them transition to adult care and gain independence in their own care remain unanswered questions.

Methods: The aims of the dissertation address the following questions: Chapter 1) what are the common diagnoses at death and what are the correlates of viral suppression among severely ill, hospitalized, antiretroviral therapy (ART) naïve HIV-positive children aged 0-12 years in Kenya? Using data from a randomized controlled trial (RCT) on urgent versus post–stabilization antiretroviral treatment (ART) (PUSH trial), we use survival analysis methods examined sociodemographic and clinical correlates of mortality. Chapter 2) What is the prevalence of viral suppression and what clinic and individual level factors are associated with viral suppression among HIV-positive adolescents and young adults (AYA) age 10-24 years, on ART for more than 6 months and enrolled in HIV care programs in Kenya? We used multilevel logistic regression methods to estimate association of viral suppression with hypothesized individual and clinic level factors. Chapter 3) What are the current adolescent transition practices in Kenya, and how can we define transition and its success in programmatic settings in Kenya. We used descriptive statistics to describe adolescent HIV care practice, disclosure and transition services in Kenya and a user-centered design workshop to develop transition definitions and key elements for programmatic use in Kenya.

Results: Chapter 1: Overall 39/181 (22%) of hospitalized HIV-positive children enrolled in the PUSH RCT died. Pneumonia or suspected tuberculosis, and gastroenteritis were the most common diagnoses at the time of death. Young age (<2 years) and being an orphaned or vulnerable child (OVC) were independently associated with mortality. Chapter 2: Among 9921 AYA enrolled in 99 facilities, 2664 (27%) had unsuppressed viral load. Adjusting for clinic and individual factors, young age (10-24 and 15-19), perinatal HIV infection, male sex and increasing duration on ART were associated with poor viral suppression. Adolescents in clinics with separate adolescent spaces, lower-level clinic, and faster viral load turnaround time were more likely to have viral suppression. Chapter 3: The majority of HIV clinics in Kenya had included models of care to meet specific adolescent needs. Adolescent days, most on weekend days were common. Transition definitions were heterogeneous, and tracking systems had limited ability to monitor individual progress or assess outcomes.

Conclusions: The findings of this dissertation emphasize on the need to develop strategies to identify HIV infected children early and link them to care, and to optimize hospital management for severely ill children. As children grow into adolescence, strategies to aggressively identify and manage virologic failure are needed particularly for perinatal infected AYA. At program level, consistent transition definitions and defining measures of success are first steps in

studying transitional care. Tools to support HIV disclosure services and support adolescents gain skills and knowledge they need to independently manage their care are needed.

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INTRODUCTION

In 2017, UNAIDS estimated that there were 1.8 million children and young adolescents (age 0-15) living with HIV[1]. While the number of pediatric HIV infections has dramatically reduced with a 35% decline between 2010 and 2017, there were still 180,000 new pediatric infections in 2017 alone[1]. Globally, only 52% of children had access to antiretroviral therapy (ART) in 2017[1]. Pediatric HIV is an aggressive disease, and without treatment 50% of untreated children die by the age of 2 years[2-4]. Early diagnosis and antiretroviral therapy significantly improves survival, growth, and preserves neuro-development[5-8] and treatment guidelines now recommend immediate initiation of ART after diagnosis[9]. However, children continue to present late for care[10], due to gaps in prevention of mother to child HIV transmission (PMTCT) programs particularly related to incident maternal HIV infections[11,12]. For young children presenting to care with symptomatic HIV disease, the risk of mortality is three fold higher, compared to those identified at PMTCT clinics[13]. For late presenters, urgent ART treatment does not improve survival[14], but these children may benefit from optimized critical care interventions to support care at the time of hospital admission. While early diagnosis remains the cornerstone of survival for pediatric HIV, understanding diagnoses at the time of death and correlates of mortality in hospitalized children may help clinicians identify children at high risk of death and optimize their clinical management.

For children who survive pediatric HIV, they enter the adolescence period with a myriad of issues related to perinatal HIV. Historical challenges such as exposure to different ART regimens, longer duration of ART exposure, and inadequate plasma levels of ART due to unpalatable medication formulations and lack of dose adjustment as weight changes predispose them to virological failure[15,16]. Caregiver changes as a result of parental death or illness and late disclosure of HIV status influence adherence and in turn viral suppression[17,18]. Mental health issues in adolescence including depression and anxiety are common[19]. Indeed, for adolescents and young adults (AYA) age 10-24, maintaining viral suppression remains elusive for almost a third of AYA in care[20,21].

AYA mortality remains a concern, they are the only age-group in which declines in HIV mortality are not as rapid as in children or adults[22]. Limited treatment options and longevity of first line treatment regimens remain a global concern. As the number of perinatally infected adolescents continues to bulge, there is need to understand what individual and clinic factors influence viral suppression.

Challenges in care are compounded by health care systems in sub-Saharan Africa (SSA) that are not designed to recognize unique AYA challenges[23]. In SSA there are few children with chronic non-infectious conditions surviving to adolescence, and these children are largely managed in specialized care systems. Models to support these children to transition to adult clinics and develop independence in their own care are generally lacking, and these children face challenges as they enter adulthood. Health system challenges for AYA in SSA include lack of a standard definition of an adolescent, lack of age disaggregated data to understand AYA health, lack of standard protocols for adherence, retention and transition to adult care and lack of specialized adolescent health experts[23,24]. Despite these challenges, clinics have identified innovative ways to address unique adolescent needs[24,25], but studies to determine the impact of these innovations are lacking. Developing consistent transition definitions and protocols that impart knowledge and skills to support AYA become independent in care is the first step to understanding transitional care.

Chapter 1 of this dissertation assesses causes of death and cofactors of mortality among hospitalized ART naïve HIV infected children age 0-12 who presented to care with symptomatic illness. Chapter 2 examines individual and clinic level correlates of viral suppression among AYA in programmatic settings in Kenya. Chapter 3 fills in gaps in transition research in SSA by describing current models of AYA care and transition and disclosure services available in Kenya; and provides transition definitions and key components that could be used for development of transition protocols in programmatic settings in SSA.

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CHAPTER 1: Cofactors of mortality among hospitalized HIV-infected children initiating ART in Kenya

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ABSTRACT

Objectives: Identifying factors associated with mortality among acutely ill HIV-infected children presenting with advanced HIV disease may help clinicians optimize care for those at highest risk of death.

Design: Using data from a randomized controlled trial **(**NCT02063880)**,** we determined baseline socio-demographic, clinical, and laboratory cofactors of mortality among HIV-infected children in Kenya**.**

Methods: We enrolled hospitalized, HIV-infected, ART-naïve children (0-12 years) and followed them for 6 months. We used Cox proportional hazards regression to estimate hazard ratios for death and 95% confidence intervals (CI).

Results: Of 181 enrolled children, 39 (22%) died. Common diagnoses at death were pneumonia or suspected pulmonary TB (23 [59%]) and gastroenteritis (7 [18%]). Factors associated with mortality in univariate analysis included age <2 years (hazard ratio [HR] 3.08 [95% CI 1.50 to 6.33]), orphaned or vulnerable child (OVC) (HR 2.05 [95%CI 1.09 to 3.84)], weight-for-age Z-score (WAZ) <-2 (HR 2.29 [95%CI 1.05 to 5.00]), diagnosis of pneumonia with hypoxia (HR 5.25 [95%CI 2.00 to 13.84]), oral thrush (HR 2.17 [95% CI 1.15 to 4.09]), persistent diarrhea (HR 3.81 [95% CI 1.89 to 7.69]) and higher $\log_{10}$ HIV-1 viral load (HR 2.16 (95% CI 1.35 to 3.46]) (all $p<0.05$). In multivariable analysis, age under <2 years and OVC status remained significantly associated with mortality.

Conclusions: Young age and OVC status independently predicted mortality. Hypoxic pneumonia, oral thrush and persistent diarrhea are important clinical features that predict mortality. Strategies to enhance early diagnosis in children and improve hospital management of critically ill HIV-infected children are needed.

INTRODUCTION

Early diagnosis and initiation of antiretroviral therapy (ART) among HIV-infected children dramatically improves survival [26]. However, many children in sub-Saharan Africa first present for care severely ill, and mortality remains high despite prompt ART initiation [10,27,28]. Identifying factors associated with mortality may enable clinicians to recognize and optimize clinical management. Previous studies have identified various factors associated with mortality in HIV-infected children initiating ART, who are hospitalized and in outpatient clinics. Known correlates of mortality include younger age, immunosuppression, poor growth, hospitalization diagnoses of anemia, pneumonia or gastroenteritis, high viral loads and low CD4 count or CD4% [10,29-33]. ART initiation in acutely ill hospitalized children remains uncommon, with clinicians in most settings delaying ART until children stabilize; this approach is associated with high pre-ART mortality[10]. With the current WHO recommendation to start ART even earlier in critically ill children [24], it is important to identify correlates of mortality in severely ill children to optimize supportive care.

Within a clinical trial on timing of ART initiation, we aimed to determine correlates of mortality.

METHODS

The Pediatric Urgent Start of HAART (PUSH) study was a randomized clinical trial (RCT) of urgent versus post-stabilization ART among hospitalized HIV-infected children newly initiating ART in 4 hospitals in Kenya[27]. The enrollment period was between April 2013 and May 2015, with follow-up completed in November 2015. RCT eligibility criteria were: age 0-12 years, confirmed HIV-positive, ART naïve, caregiver planning to reside in catchment area for next 6 months, eligible for ART, and caregiver willing to give informed consent. Children with confirmed or suspected central nervous system infection were excluded. HIV diagnosis for children <18 months (using PCR assays) was performed within study with turnaround time of 48 hours. The study was approved by the University of Nairobi / Kenyatta National Hospital (UoN/KNH) Ethics Research Committee (ERC) and the University of Washington Institutional Review Board (IRB).

Baseline medical history, and laboratory information were collected at enrollment. Hospitalized children were managed for coinfections by hospital staff using Kenya Ministry of Health pediatric protocols[34]. Briefly, children with severe pneumonia received high dose oral cotrimoxazole and intravenous antibiotics. Dehydration was managed with intravenous ringer's lactate or oral rehydration solution as appropriate. Malnutrition and dehydration were managed using rehydration solutions for malnutrition, and F75/F100 feeding regimens. Oral fluconazole (IV fluconazole was not available) was used for oral thrush. First line ART consisted of a backbone of abacavir, lamivudine and efavirenz (EFV) for children >3 years or more than 10 kilograms (kg) or nevirapine (NVP) for children <3 years or < 10 kg and who were not exposed to NVP for PMTCT, or lopinavir/ritonavir (LPV/r) for children <3 years if exposed to NVP. Incidence of mortality, immune reconstitution inflammatory syndrome (IRIS), and proportion with drug toxicity did not differ by randomization arm[27].

Outcome

Data on mortality was collected from hospital records or interviews with caregivers when death occurred outside participating hospitals.

Correlates of mortality

We considered the following pre-specified correlates of mortality: age (≧2 and ≤2 years), weight-for-age Z-score (WAZ) (≥-2SD and <-2SD), height-for-age Z (HAZ) score (≥-2SD and <-2SD), weight-for-height Z score (WHZ) (≥-2SD and <-2SD), $\log_{10}$ viral load, severe immunosuppression (defined using CD4% thresholds by age[35] [<12months <30%, 12-35 months <25%, 36-59 months <20%, over 5 years <350 cells/ul]) and hospital admission diagnoses. Growth Z scores were calculated using the WHO reference population [36,37]. Additional correlates considered in exploratory analysis included: orphaned and vulnerable child (OVC) status (defined as orphaned by both parents or in a single parent family), prior HIV diagnosis, visible wasting, diagnoses of pneumonia, pneumonia with hypoxia, suspected TB, oral thrush, diarrhea, and malaria, baseline

WHO stage, CD4%, confirmed TB diagnosis, WHO stage, and hemoglobin (g/dL), albumin (g/L) and C-reactive protein (CRP) (mg/dl).

Statistical analysis

We summarized baseline characteristics using medians, interquartile ranges (IQR), and proportions. We used Cox proportional hazards regression to compare hazard ratios (HR) in subgroups. In multivariable analysis, we included cofactors that were associated with mortality on univariate analysis ($p<0.1$) and were not collinear with other variables (standard error did not change by more than 10%). We considered p-values of ≤ 0.05 to be statistically significant. All analysis was conducted using Stata version 14 (StataCorp, College Station, Texas, USA).

RESULTS

Of 250 HIV positive children identified, 181 (72%) met eligibility criteria [27]. Median age was 1.9 years, 81 (45%) were female, [27], over half (94 [52%]) were <2 years, 64 (36%) children were OVC, and 62 (34%) were breastfeeding. Of 95 with information on nutritional supplementation, 32 (34%) received F75 (78%), F100 (16%), or ready to use therapeutic food (RUTF) /infant formula (6%). Of 42 (23%) who had tested HIV positive previously, median age was 1.8 years (IQR: 1-4), time since diagnosis 3.4 months [IQR: 1.4 to 7.4], and 21 (50%) had previously enrolled in HIV care. Of 172 with PMTCT information, 58 (34%) mothers were HIV positive during pregnancy and 32 (54%) received ART.

Over half (65%) had WAZ less than -2SD[27]; 64 (47%) and 109 (61%) had WHZ<-2SD and HAZ<-2SD, respectively. Two thirds (65%) had pneumonia[27], and 25% of them were hypoxic (oxygen saturations <90%). Of the 118 children with pneumonia at admission, 96 (81%) had chest x-ray results. Of these, 27 (28%) had radiological evidence of TB and 36 (38%) of pneumonia. Of those with pneumonia, 81 (79%) met respiratory rate (RR) criteria for pneumonia per national protocols in those <5 years or had RR>30 in those over 5 years, and 35 (80%) had oxygen saturation <90%. Twenty-seven (15%) had suspected TB, 13 (7%) had laboratory-confirmed TB[27], 53 (29%) had oral thrush, 87 (48%) had diarrhea, a quarter of whom had persistent diarrhea (lasting ≥2 weeks) and almost half (41%) had dehydration. Twenty percent had malaria, 124 (69%) were in WHO stage III or IV[27] and 144 (80%) were severely immunosuppressed. Median viral load was $\log_{10}$ 5.7 (IQR 5.0, 6.3), 15 (8%) had severe anemia (hemoglobin <6 g/dl). Median serum albumin and CRP were 32 g/L (IQR 26, 40) and 13 mg/dL (IQR 3, 48), respectively. Children with oral thrush were more likely to be severely malnourished (p= 0.022) and severely immunosuppressed (p <0.001).

Overall, 39 (22%) died; Seven (18%) died by day 1 of enrollment, 14 (36%) by day 3, 28 (72%) by day 14 and 33 (85%) by day 28. Median age of those who died was 1.3 years (IQR 0.5 to 2.1). Median days between admission and death was 8 days (IQR 5 to 20). Six-month cumulative probability of survival was 0.78 (95% CI 0.71-0.83) with majority of deaths 31 (79%) occurring in study hospitals. Pneumonia or suspected TB were the primary diagnoses at the time of death in the majority (23 [59%]). Compared to those who died later, children who died in the first 2 weeks were more likely to have oral thrush (p=0.041).

Correlates associated with mortality in univariate analysis included: age ≤2 years (HR 3.08 [95% CI 1.50 to 6.33] p= 0.002), OVC status (HR 2.05 [95% CI 1.09 to 3.84] p= 0.025), WAZ scores below -2, or -3 (HR 2.29 [95% CI 1.05 to 5.00] p= 0.037 and HR 2.22 [95% CI 1.16 to 4.26] p= 0.016, respectively), pneumonia with hypoxia (HR 5.25 [95% CI 2.00 to 13.84] p=0.001), oral thrush (HR 2.17 [95% CI 1.15 to 4.09] p=0.016), persistent diarrhea (HR 3.81 [95% CI 1.89 to 7.69) p<0.001) and higher $\log_{10}$ viral load (HR 2.16 [95% CI 1.35 to 3.46) p=0.001). Malaria was associated with lower hazard of death (HR 0.30 [95% CI 0.09 to 0.99) p= 0.048) (Figure 1) (Table 1).

In the multivariable model age <2 years (HR 3.33 [95% CI 1.57 to 7.07) p= 0.002) and OVC status (HR 2.06 [95% CI 1.09 to 3.90) p= 0.027) remained independently associated with mortality, with a trend towards significance for WAZ <-2 (HR 2.10 [95% CI 0.96 to 4.60) p=0.064).

In sensitivity analysis including only those who died in first 2 weeks, there was an increased HR for: WAZ <-2 (4.67 [1.41 to 15.5 p=0.012), pneumonia with hypoxia (6.78 [2.04 to 22.5 p=0.002), and oral thrush (3.15 [1.50 to 6.62 p=0.002). Excluding the 7 children who died in the first 24 hours did not change appreciably change of the hazard ratios (supplementary table 1 and 2).

DISCUSSION

We observed high early overall mortality with the majority of deaths occurring among children with pneumonia.

High early mortality has been described in late-presenting and hospitalized adults and children [10,28,29,31,38]; underscoring the need for enhanced interventions for critical care. More aggressive management of suspected co-infections such as presumptive treatment for TB, candida and protozoa among those with diarrhea, in addition to broad spectrum antibiotics may improve outcomes. However, such an intervention package would need to balance potential challenge of antibiotic resistance, pill burden, drug interactions and challenges of administration in young children. Supportive care including pulse oximetry, oxygen delivery and management of dehydration, in addition to access to quick and accurate diagnostics to tailor treatment regimens are also critical. While a prophylaxis intervention package has been found effective in adults and older children[39], studies to assess interventions to prevent mortality in hospitalized younger children are lacking.

Early diagnosis and initiation of treatment prior to severe illness is critical for survival. We previously reported system gaps in the PMTCT cascade in this cohort with undiagnosed maternal infection and maternal seroconversions contributing to the largest gap[40]. Reliance on laboratory-based confirmation of HIV status, and long result turnaround times impact timely initiation of antiretroviral therapy [41]. Despite prioritized PCR testing ART initiation was still delayed by about 2 days [27]. In routine clinical care, point-of-care testing platforms for earlier diagnosis for critically ill children could accelerate timely diagnosis and treatment in children [42].

Bacterial pneumonia is the leading cause of death in children [43-45]. *Streptococcus pneumonia* and *Hemophilus influenza*, the most common causes, are responsive to recommended first line antibiotics (penicillin/gentamicin) used in our study[46]. Supportive management with pulse oximetry monitoring and oxygen supplementation are critical. However, pulse oximetry monitoring is not widely used in resource-limited settings[47]. Pneumocystis or CMV pneumonia were likely cause of hypoxic pneumonia and children with pneumonia were treated with high-dose cotrimoxazole to address pneumocystis, identifying hypoxia and aggressive oxygen management including continuous positive airway pressure (CPAP) and intubation may prevent mortality.

While TB is an important cause of respiratory deaths in children [48], diagnosis remains problematic due to low test sensitivity, with a large number of children classified as unconfirmed TB despite intensive case finding [44,49,50]. Efforts to rapidly diagnose TB are needed. We recently demonstrated that stool GeneXpert had similar sensitivity to sputum geneXpert, and urinary LAM tests had higher sensitivity among immunosuppressed children; adoption of these strategies may improve case detection for children [51].

Cryptosporidium, enteropathogenic E.coli (EPEC), protozoa such as amoeba, and CMV enteritis, are causes of diarrhoea in HIV-infected children [52,53]. Broad spectrum antibiotics used in 79% of the children in our study [3] may have provided antibiotic coverage for EPEC. Studies on identification of treatment options for cryptosporidium are needed. In addition, appropriate fluid management is critical.

Consistent with other studies, young age, higher viral load, malnutrition and severe immunosuppression predicted mortality [29-31,54,55]. Risk of death was higher in OVC, and could possibly be related to late diagnosis and socioeconomic challenges that lead to chronic malnutrition [56], though we did not observe higher malnutrition in OVC. Disseminated candidiasis and malnutrition may have resulted in death among children with oral thrush. However, children had multiple co-morbidities making it difficult to clearly define mechanism of mortality.

HIV diagnosis was confirmed earlier than standard-of-care approaches for children, enabling evaluation of early cofactors of mortality. Actual cause of death could not be determined as postmortem examinations were not conducted.

We found that young age and OVC status were important cofactors of mortality. Hypoxic pneumonia, oral thrush and persistent diarrhea are important diagnoses that may predict mortality. Strategies to diagnose children early and enhance critical care management and treatment for HIV-infected children are urgently needed.

TABLES AND FIGURES

Table 1: Correlates of mortality (univariate analysis)

		Deaths/person years	Incidence per 100 person years	Univariate analysis HR (95% CI)	Univariate analysis p value
Characteristic					
Age	< 2 years	29/28.7	101 (70, 145)	3.08 (1.50, 6.33)	0.002
	≥ 2	10/35.0	29 (15, 53)	Ref	
OVC status	OVC	20/20.3	98 (63, 152)	2.05 (1.09, 3.84)	
	Not OVC	19/42.9	44 (28, 69)	Ref	0.025
Previously HIV positive	Yes	9/15.9	57 (29, 109)	0.92 (0.44, 1.94)	
	No	30/47.8	63 (44, 90)	Ref	0.83
Nutritional status					
WAZ	< -2 SD	30/36.4	82 (58, 118)	2.29 (1.05, 5.00)	0.037
	≥ -2 SD	8/24.9	32 (16, 64)	Ref	
WHZ	< -2 SD	18/20.5	88 (55, 139)	1.65 (0.81, 3.37)	0.168
	≥ -2 SD	13/25.3	51 (30, 89)	Ref	
HAZ	< -2 SD	25/37.6	67 (45, 98)	1.52 (0.75, 3.08)	0.251
	≥ -2 SD	11/26.0	42 (23, 76)	Ref	
Visibly wasted	Yes	26/31.3	83 (57, 122)	1.94 (1.00, 3.78)	0.051
	No	13/32.4	40 (23, 69)	Ref	
Enrollment diagnosis					
Pneumonia	Yes	23/41.8	55 (37, 83)	0.76 (0.40, 1.44)	0.396
	No	16/21.9	73 (45, 119)	Ref	
Pneumonia with hypoxia	Yes	10/6.4	156 (84, 289)	5.25 (2.00, 13.84)	0.001
	No	7/30.4	23 (11, 48)	Ref	
Suspected pulmonary TB	Yes	4/10.7	37 (14, 99)	0.60 (0.21, 1.70)	0.341
	No	35/52.1	67 (48, 94)	Ref	
Oral thrush	Yes	17/15.9	107 (67, 172)	2.17 (1.15, 4.09)	0.016
	No	22/47.9	46 (30, 70)	Ref	
Diarrhea	Yes	21/29.7	71 (46, 109)	1.34 (0.71, 2.51)	0.365
	No	18/34.1	53 (33, 84)	Ref	
Persistent diarrhea	Yes	11/4.6	240 (133, 433)	3.81 (1.89, 7.69)	<0.001
	No	28/59.1	47 (33, 69)	Ref	
Malaria	Yes	3/14.7	20 (7, 63)	0.30 (0.09, 0.99)	0.048
	No	36/48.5	74 (54, 103)	Ref	
Baseline WHO stage	Stage III/IV	31/41.1	75 (53, 107)	1.90 (0.87, 4.13)	0.106
	Stage I/II	8/22.1	36 (18, 72)	Ref	

Laboratory					
CD4% <15%	Yes	21/32.1	65 (43, 100)	1.16 (0.62 to 2.18)	0.645
	No	18/31.2	58 (36, 92)	Ref	
CD4% <10%	Yes	14/17.9	78 (46, 132)	1.37 (0.71 to 2.64)	0.343
	No	25/45.5	55 (37, 81)	Ref	
Confirmed TB	Yes	6/3.6	169 (76, 376)	--	0.053[1]
	No	33/60.2	55 (39, 77)	--	
Severe immunosuppression[2]	Yes	34/49.6	69 (49, 96)	1.79 (0.70 to 4.58)	0.224
	No	5/13.7	36 (15, 88)	Ref	
Hemoglobin	<6g/dL	2/5.8	34 (9, 137)	0.58 (0.14 to 2.42)	0.457
	≥6g/dL	37/57.9	64 (46, 88)	Ref	
Albumin	<30 g/L	19/22.7	84 (53, 131)	1.73 (0.90 to 3.32)	0.102
	≥30 g/L	17/35.9	47 (29, 76)	Ref	

[1]Log-rank test p value (proportional hazards assumption not met) [2] defined by age and CD4 threshold by WHO definitions

Supplementary material

Supplementary table 1: Univariate analysis excluding children who died in the first 24 hours

	Univariate analysis overall	**Univariate analysis excluding the 7 who died in first 24 hours**
Characteristic	**HR (95% CI), p-value**	**HR (95% CI); p-value**
Age under 2 years	3.08 (1.50, 6.33); 0.002	3.28 (1.47, 7.31); 0.004
OVC	2.05 (1.09, 3.84); 0.025	1.98 (0.99, 3.96); 0.054
Previously HIV positive	0.92 (0.44, 1.93); 0.83	1.01 (0.45, 2.24); 0.987
WAZ <-2SD	2.29 (1.05, 5.00); 0.037	2.61 (1.07, 6.35); 0.035
WHZ <-2SD	1.65 (0.81, 3.37); 0.168	1.65 (0.76, 3.58); 0.209
HAZ <-2SD	1.52 (0.75, 3.08); 0.251	1.57 (0.72, 3.43); 0.257
Visibly wasted	1.94 (1.00, 3.78); 0.051	2.15 (1.02, 4.54); 0.045
Pneumonia	0.76 (0.40, 1.44); 0.396	0.68 (0.34, 1.36); 0.273
Pneumonia with hypoxia	5.25 (2.00, 13.84); 0.001	4.54 (1.52, 13.5); 0.007
Suspected TB	0.60 (0.21, 1.70); 0.341	0.54 (0.16, 1.77); 0.310
Oral thrush	2.17 (1.15, 4.09); 0.016	2.26 (1.12, 4.55); 0.022
Gastroenteritis	1.34 (0.71, 2.51); 0.365	1.49 (0.74, 3.00); 0.260
Persistent diarrhea	3.81 (1.89, 7.69); <0.001	4.74 (2.24, 10.04); <0.001
Malaria	0.30 (0.09, 0.99); 0.048	0.24 (0.06, 1.00); 0.050
WHO stage 3 and 4	1.90 (0.87, 4.13); 0.106	2.16 (0.89, 5.25); 0.089
CD4% <15%	1.16 (0.62 to 2.18); 0.645	0.88 (0.44, 1.77); 0.728
CD4% <10%	1.37 (0.71 to 2.64); 0.343	1.11 (0.53, 2.35); 0.780
Confirmed TB*	p=0.053	p=0.01*
Severe immunosuppression	1.79 (0.70 to 4.58); 0.224	1.86 (0.65, 5.31); 0.244
Log $_{10}$ viral load	2.16 (1.35 to 3.46); 0.001	2.01 (1.23, 3.29); 0.005
Hemoglobin less than 6g/dl	0.58 (0.14 to 2.42); 0.457	p=0.27*
Albumin less than 30 mg/dl	1.73 (0.90 to 3.32); 0.102	2.23 (1.07, 4.68); 0.033

HR not estimated, proportional hazards assumption not met

Supplementary table 2: Characteristics of children who died in the first 2 weeks versus later

Characteristics	n(%) or median (IQR)	n(%) or median (IQR)
	Died early (first 2 weeks) (n=18)	**Died later (n=21)**
Under 2 years	14 (78%)	15 (71%)
OVC status	11 (61%)	9 (43%)
Previously HIV positive	4 (22%)	9 (43%)
Currently breastfeeding	7 (41%)	11 (52%)
WAZ score < -2 SD	15 (83%)	15 (75%)
Oral thrush	11 (61%)*	6 (29%)*
Persistent diarrhea	6 (33%)	5 (24%)
Pneumonia	11 (61%)	12 (57%)
With hypoxia (oxygen <90%)	7 (70%)	3 (43%)
Confirmed TB	0	6 (29%)
Severe immunosuppression	15 (83%)	19 (90%)
Log 10 viral load	6.2 (5.8, 6.6)	5.9 (5.5, 6.6)

*p<0.05

CHAPTER 2: Individual and clinic level correlates of viral suppression among HIV infected adolescents and young adults in Kenya

ABSTRACT

Objectives: Understanding correlates of viral suppression among HIV positive adolescents and young adults (AYA) is critical for developing interventions.

Design: We determined individual-level and clinic-level factors associated with viral suppression among AYA age 10-24 years in Kenya.

Methods: We abstracted medical records of AYA living with HIV on antiretroviral therapy (ART) for >6 months, enrolled in care between January 2016-December 2017 in 99 clinics throughout Kenya, and collected information on clinic services. We used multi-level logistic regression models to determine correlates of viral suppression.

Results: Among 9921 AYA on ART >6 months, 2664 (27%) had unsuppressed viral load (VL) at last test. Adjusting for clinic-level factors, AYA who were young (10-14 or 15-19) had 37% (95 CI: 29-45) and 40% (95% CI: 31-47) lower odds of suppression than AYA 20-24 years. Male AYA had 30% (95%CI: 22-37%) lower odds of suppression than female, and significantly poorer viral suppression was seen in males in all age sub-groups. Longer ART duration was associated with lower odds of suppression among those on ART for 2-5, 5-10 and >10 years compared to those on ART for 6-12 months ($p<0.001$). Individual-level factors exerted more influence on VL suppression than clinic-level factors. Important clinic-level correlates of better suppression included designated adolescent spaces, type of clinic (mission/foundation), and clinic location in high prevalence counties. Longer VL turnaround time (TAT) was associated with lower odds of suppression (OR: 0.94 [95% CI 0.92, 0.97] per 10-day increase).

Conclusions: Individual-level characteristics (young age, male sex, longer ART duration) were associated with poor viral suppression. Adolescent-space and shorter VL TAT were associated

with improved viral suppression. Supporting AYA at-risk for poor suppression and incorporating clinic best-practices could improve outcomes.

INTRODUCTION

Adolescents and young adults (AYA) living with HIV are at high risk of virologic failure and mortality[22,57]. AYA are twice as likely to have unsuppressed viral load, have higher risk of virologic rebound and poorer adherence than adults[57]. Global viral suppression rates among AYA vary widely due to differences in age disaggregation and age-period cohort effects, from 27-90%[57-62]. Viral suppression in AYA in sub-Saharan Africa (SSA) remains poorly characterized because viral load testing has only recently been introduced for routine monitoring[63] [59]. Program data from Kenya and Uganda, two of 5 countries with the highest burden of adolescent HIV found that over a quarter of adolescents age 10-19 on antiretroviral therapy (ART) for more than 6 months had viral load counts of greater than 1000 copies/ml, indicating possible virologic failure[20,21]. To achieve UNAIDS 95-95-95 goals, there is need to understand correlates of viral suppression among AYA.

Correlates of poor viral suppression among AYA in SSA include older age at full disclosure of HIV status[64], male sex[21,65], younger age likely reflecting perinatal infection[21], poor adherence[21], TB diagnosis[21], and mental health factors[21] including depression, low self-efficacy and poor social support. AYA in SSA are a mixed population with an estimated 56% of 10-14 year olds and 86% of 15-19 year olds perinatally and behaviorally infected, respectively[66]; and viral suppression differs by mode of infection[57,60]. Differentiating perinatal and behavioral acquired HIV remains challenging due to missing information on maternal HIV status. Age cut-off used (ART initiation at age ≤10 or ≤12) may misclassify perinatal infections[67,68] and data on CD4 counts and height that could decrease misclassification is often lacking[69]. In addition, ART regimens and formulations in children have evolved over time, and sub-optimal ART doses[15], perinatal ART exposure and acquired drug resistance[70,71] and caregiver challenges[15,17] during childhood will influence viral suppression. As children grow to adolescence, transition to adult care contributes to poor clinical outcomes[72]. Transition in SSA remains poorly defined and its influence of viral suppression is unexplored[24].

Clinic level factors may also influence AYA outcomes. In one study, AYA in clinics in high prevalence areas had better viral suppression[73], likely as a result of more experience and resources. High clinic volumes and high AYA:staff ratios may reduce contact time which decreases opportunities to identify and address adherence. Innovations in clinic approaches to AYA in SSA have evolved over time, with different models of care emerging to meet the needs of AYA and support their independence to adult services[24,25]. These models include AYA clinic days[24,25,74], weekend AYA clinic days[75] and additional non-clinical AYA-focused activities[24]. AYA-focused training, tools to track milestones and topics to explore at clinic visits have also been developed[76]. For most of these innovations impact on clinical outcomes remains unknown. Tracking tools and down-referral of stable AYA from specialist to primary care clinics have been associated with increased viral suppression[77,62]. Understanding clinic-level factors associated with viral suppression can help clinics to adapt approaches that offer more benefit to AYA.

The Kenya national viral load (VL) program[20], implemented in 2014, provides a centralized VL database to comprehensively describe viral suppression, including among AYA. We aimed to determine individual and clinic level correlates of viral suppression among HIV positive AYA enrolled in HIV care in program settings in Kenya in 2016-2017.

METHODS

Study design

This study was conducted in the context of a larger study aimed at understanding transition practices in Kenya (Adolescent Transition to Adult Care for HIV infected adolescents [ATTACH] [NCT03574129]). Participating clinics were randomly selected from all clinics using electronic medical records (EMRs) in 2015 which had at least 300 clients ever enrolled in care. These estimates were designed to include clinics that had at least 30 AYA age 10-19 enrolled in care.

At data pull, the actual number of AYA was unknown as clinics in SSA typically do not disaggregate data by AYA specific age groups. Overall, 590 clinics met inclusion criteria. These were divided into tertiles based on the total clinic population and 34 clinics randomly selected from each of the small, medium and large tertile clinics. This approach allowed inclusion of different clinic sizes in the final sample. A total of 102 clinics throughout Kenya were selected.

Ethical considerations

The study was approved by the University of Washington (UW) Institutional Review Board (IRB) and the Kenyatta National Hospital (KNH) University of Nairobi (UoN) Ethical Review Committee (ERC). In addition, approval from the Kenya Ministry of Health National AIDS and STI Control Program (NASCOP), County Departments of Health and managers of participating clinics was obtained.

Viral load data

Viral load data was obtained from clinic records in the national VL program[20]. The study team accessed VL records of AYA age 10-24 during the period January 1, 2016 to December 31, 2017. Typically, patient information on current age, sex, ART regimen, ART initiation date, reason for VL request, data of sample collection, processing and dispatch, and clinic identifiers (name of clinic, unique number and county) is collected at sample collection. Date of birth is also collected in some clinics. Samples then accompany the data and records are updated with the VL result including information on whether the sample was acceptable, the actual VL result and a comment on whether the result is a suppressed or unsuppressed VL. Viral suppression is defined as VL of >1000 copies/ml. The lower limit of detection varies, at 40, 250 or 550 copies/ml and is recorded either as LDL (lower than detection limit) or as actual limit. Clinics can access results through a secure link to the national program. The data is then transferred to individual patient records. To obtain the most recent and accurate records available, the study utilized results obtained from the national VL program. VL records of AYA who were on ART for less than 6 months or were missing ART duration were excluded. All data was abstracted between January and December 2018.

Clinic data

In participating facilities, data on clinic size, staffing, models of adolescent care, and adolescent services was collected (data from the survey is reported separately). Information was obtained after written informed consents from clinic managers responsible for adolescent HIV care and who had been in the clinic for at least 6 months prior to the interview. In-person or telephone interviews were conducted and data was recorded in paper records and then entered into a REDCap[78] database.

Data analysis

Continuous data was summarized using medians and interquartile ranges (IQR) and categorical data using counts and proportions. Variables of interest from the VL database included: Age (classified as 10-14, 15-19 and 20-24 years), sex (male or female), ART duration in years (categorized as 6-12 months, 1-2, 2-5, 5-10 and over 10 years) and ART regimen (NNRTI based, PI based, other). Proportions perinatally infected were estimated using an age cut-off of age 12 at ART initiation[60]. Clinic level factors considered included number of adolescents in care, clinic category (County, sub-County, health center/dispensary, mission/foundation), number of AYA in follow-up, AYA:health care worker ratio, HIV clinic staffing (availability of a nutritionist, social worker or community health worker) AYA model of care (AYA clinic days, weekend clinics, incentives), separate adolescent clinic space, staff training on AYA, use of the adolescent checklist[76], all day versus half day clinics, ability to identify adolescent records, availability of mental health screening tools and participation in community or school activities. County HIV prevalence information was obtained from county estimates, and classified as hyper endemic, high, medium or low endemicity per national classification (prevalence >11.1, 5-11%, 2-4.9% and <2%, respectively)[79]. Viral suppression was defined using the last ever recorded VL with levels of

$>$ or $\leq$ 1000 copies/ml defined as unsuppressed or suppressed, respectively, per national guidelines[80].

Univariate analysis estimating the OR (and 95% confidence intervals [CI]) for viral suppression for each of the individual level factors, and clinic level factors were conducted. Multilevel models using mixed effects logistic regression with random clinic level intercepts to estimate odds ratio (OR) of hypothesized correlates of viral suppression with level 1 factors (individual factors) and level 2 factors (clinic factors) were used. The first model considered was the unconditional (null model) that estimated if there was a significant difference between and within clinic effect of viral suppression. The second model added in individual level factors and the third both individual and clinic level factors after exclusion of collinear variables. Variables were defined as collinear if after addition of the second variable, the standard error changed by more than 10%. Odds ratios and 95% confidence intervals and intraclass correlation (ICC) were reported. All data analysis was conducted using STATA version 14.

RESULTS

A total of 20056 VL records were abstracted; 2162 (11%) non-routine VL or those done for unknown reasons were excluded. A further 2509 records of AYA on ART for less than 6 months or missing ART duration were excluded. Of 9921 individual adolescent records, 2664 (27%) had unsuppressed VL at their last recorded VL test (Figure 1).

A total of 3397 (34%), 2315 (23%) and 4209 (43%) were in the 10-14, 15-19, and 20-24 year age-group, respectively. The majority (69%) were female and 4339 (44%) were categorized as perinatally infected. Almost all (8865 [90%]) were on first line non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens. A majority had been on ART for a median of 2-5 years (3213 [31%]), 5-10 years (2683 [27%]) or 1-2 years (1933 [20%]) (Table 1).

VL records from 99 clinics were included; 3 clinics were excluded as their VL data lacked information on ART duration. Of these, 27(26%), 14(14%), 55 (56%) and 3 (3%) were in counties classified as hyper-endemic, high, medium or low prevalence counties. The median number of AYA per clinic was 61 (IQR: 36, 130) with an AYA:HCW ratio of 6 (IQR 3, 10). Over half of the clinics had nutritionists (62%), laboratory staff (75%) and community health workers (66%) and fewer had social workers (37%). The majority of the clinics had adolescent days, with weekend days common (57%). Separate adolescent spaces were uncommon (18 [18%]). Few clinics were open all day (25%), and almost half participated in school or community HIV activities (42% and 47%, respectively) (Table 1).

In univariate analysis, AYA age 10-14 years and 15-19 years had 50% (95%CI: 44% to 55%) (OR: 0.50 [95%CI: 0.44, 0.55]) and 51% (95%CI: 45% to 57%) (OR: 0.51 [95%CI: 0.45, 0.57]), respectively, lower oddS of viral suppression compared to AYA age 20-24 ($p<0.001$). Compared to females, males had 58% (95%CI 53%, 64%) (OR: 0.58 [95%CI: 0.53, 0.64]) lower odds of suppression ($p<0.001$). Perinatally infected AYA had 57% (95% CI 52%, 62%) (OR: 0.57 [95%CI: 0.52, 0.62]) lower odds of viral suppression compared to horizontally-infected AYA ($p<0.001$).

There was no difference in viral suppression by ART regimen. Compared to those on ART for 6-12 months, the odds of viral suppression significantly decreased with increasing duration on ART (Chi^2 test for trend p<0.001), with significant differences in the 2-5, 5-10 and over 10-year duration, respectively. Longer viral load result turnaround time (TAT) was associated lower odds of viral suppression (OR 0.95 [95%CI: 0.92, 0.97] for every 10-day increase) (Table 2).

Low County HIV prevalence (OR: 0.47 [IQR: 0.32, 0.74] p<0.001), and having a social worker (OR: 0.79 [IQR: 0.67, 0.93] p=0.005), were significantly associated with poor viral suppression, while being in a health center/dispensary (OR: 1.35 [IQR: 1.08, 1.69] p=0.008), or mission/foundation clinic (OR: 1.95 [IQR: 1.19, 3.21] p=0.008) was associated with better suppression compared to County clinics (Table 2).

In multivariate analysis, age 10-14 years, 15-19 years, male sex and longer ART duration remained significantly associated with lower odds of viral suppression both in the model with addition of individual level factors and the model with clinic level factors. Attending clinics with a social worker remained significantly associated with lower odds of suppression, and being in a mission/foundation hospital (OR: 1.27 [IQR: 1.03, 1.56] p=0.022) or where there was separate adolescent space (OR: 1.27 [95%CI: 1.03, 1.56]) were associated with higher odds viral suppression (Table 2). The social worker effect remained only among perinatally infected AYA in stratified univariate analysis (data not presented). The proportion of variance explained by clinic alone (null model) was 3% (95% CI: 2-5), and substantially decreased with the addition of individual level factors 0.4% (95% CI: 0.05-2) (Table 2b).

In stratified univariate analysis, males of all age group were significantly lower odds of viral suppression compared to females, and lower odds of suppression with longer ART duration was more pronounced in the 20-24 year olds (Figure 2: Panel A). Stratified by sex, similar patterns of viral suppression were observed in both males and females, with more pronounced effects of lower suppression among those with perinatal infection and longer ART duration in females (Figure 2: Panel B).

Overall, 14 (14%) clinics had >80% of AYA with viral suppression, 48 (48%) 70-80% and 25 (25%) <70%. Higher suppression clinics had higher County prevalence, were in lower level clinics, had non-weekend adolescent days and had faster viral load results turnaround time. Characteristics of clinics stratified by suppression status are summarized in Table 3.

DISCUSSION

In this study, we observed high overall poor viral suppression among AYA aged 10-24 years. Individual level factors including age-groups 10-14, and 15-19, male sex, perinatally acquired HIV, and longer ART duration were associated with lower odds of suppression. At the clinic level, AYA in clinics in Counties with lower HIV prevalence, lower level facilities or mission/foundation hospitals and those in clinics with separate AYA spaces had higher odds of viral suppression while those and in clinics with social workers had lower odds of suppression. Clinics with >80% of AYA virally suppressed were in higher prevalence regions, had shorter VL turnaround time (TAT), and were mission/foundation or lower level facilities.

Similar to other studies, we found that younger AYA were less likely to be virally suppressed than older AYA[20,21]. This could be due to the large proportion of perinatally infected children in the younger age-groups. Pediatric HIV care challenges include unpalatable medication, inaccurate dosing due to rapid weight changes or difficulties administering treatment which contribute to inadequate blood ART levels and drug resistance[16,81]. Parental loss or illness, challenges with disclosure and stigma and an overall higher risk of transmitted or acquired drug resistance, contribute to virologic failure[17,18,81]. Nasuuma et al recently demonstrated that intensive adherence interventions only resulted in re-suppression in 23% of children and adolescents[82], compared to 70% in adults, which may reflect the higher likelihood of resistant virus in children and adolescents [83]. Overall viral suppression status in our study was well below UNAIDS 95-95-95 targets. Only

14 (14%) of clinics had clinic viral suppression levels of >80%. With the growing population of perinatally infected children surviving to adolescence and an almost equal distribution of perinatally and horizontally infected AYA[84], there is need to re-evaluate protocols around viral suppression, look beyond adherence, and adopt a more aggressive approach to manage treatment failure in this population. A key global concern is the limited treatment options available for children and AYA; adherence support remains critical, but must be accompanied by appropriate and timely ART regimen switch particularly for perinatally infected AYA.

We found that male sex was independently associated with poor viral suppression. In the overall analysis, this could be partially due to a higher proportion of male AYA having perinatal HIV infection than female AYA. However, we found that in age-stratified analyses male AYA had poorer VL suppression than female AYA in all age groups. Among adults in SSA, there is good evidence of poor viral suppression among males[21,85,86]. This was initially thought to be a result late presentation, poor adherence, and higher substance abuse among males. However, there is emerging evidence of possible biological differences in drug metabolism[87]. Boulle et al found that males in Cameroon were more than twice as likely to have poor viral suppression even after adjusting for plasma drug concentrations[85]. Male sex has been associated with non-suppression in several pediatric studies in SSA[21,65]. However, in a study from South Africa, sex differences were noted in regimen-related CD4 recovery and cholesterol but not viral suppression[88]. Among perinatally and behaviorally infected AYA in Canada and the US, no difference[89] or an opposite effect, with males more likely to suppress, was observed [90,91]. Further studies which include standardized age-cutoffs and maternal HIV status will be useful to better understand potential sex differences in AYA viral suppression.

We hypothesized that clinic AYA care practices could result in better adherence and viral suppression. We found that designated adolescent clinic space was associated with better AYA viral suppression, however, none of the other elements in adolescent specific models of care were associated with viral suppression. Separate clinic spaces offer safe spaces that may promote discussions helpful to promote adherence. While offered in a minority of clinics, space is an important component of youth friendly services advocated for in national guidelines[92]. AYA services were available in almost all clinics, and AYA specific days were common, however, utilization of services provided in these clinics remains low[74] and clinic practices vary[24]. In addition, for viral suppression, individual level factors particularly being young, male and perinatally infected contributed more to VL suppression than clinic level factors. Counterintuitively, we found that AYA in clinics with social workers were less likely to have viral suppression. This finding may be because social workers trace out-of-care AYA who are less likely to be suppressed. While lower/medium County HIV prevalence, was not associated with lower viral suppression in adjusted analysis, high prevalence areas are associated with more care experience and more resources to support care in the US[73], and better PMTCT outcomes globally[93]. Efforts to support regions with low HIV prevalence are still needed despite challenges in resource distribution and prioritization.

We found that AYA in mission or foundation hospitals had better viral suppression, even after adjusting for AYA:HCW ratio. These facilities may have better resources in terms of leadership, space and staff motivation, and AYA activities may be more structured. More evaluation of the differences in care in these facilities could provide evidence for interventions. We found that faster VL TAT was associated with better suppression. VL testing is currently conducted in centralized facilities that are likely located in high burden areas. Transportation logistics from clinic to the laboratory may contribute to longer TAT as seen in early infant diagnosis (EID) systems, particularly with increased distance from clinic to laboratory[94]. Point of care technologies for VL testing may close the gap in TAT and could be explored particularly in low HIV-burden counties.

Our study has limitations. While we initially hoped to combine data from the VL database with individual clinic records to obtain more individual-level variables, differences in formatting unique identification numbers across clinics and databases made this process challenging. Our population is composed of AYA who were retained in care, who had samples collected for viral load testing and who were enrolled in clinics using EMRs in 2015, and therefore our results do not generalize to AYA population viral suppression. Strengths of our study include that we accessed national viral load data and accompanying clinic information from 99 clinics throughout Kenya, enabling us to evaluate critical individual and clinic level differences among AYA.

In summary, we found that age, sex, ART duration, separate AYA spaces, clinic type and VL TAT were important correlates of viral suppression. As more and more children survive pediatric HIV and move to adolescence, there is need to comprehensively address viral suppression. Clinics in low/medium prevalence counties may require additional support for better outcomes. Care approaches in mission/foundation clinics may be useful to emulate, and enhancing VL TAT or moving to point-of-care VL may enhance viral suppression in AYA.

TABLES AND FIGURES

Figure 1: Flow chart of viral load records and suppression

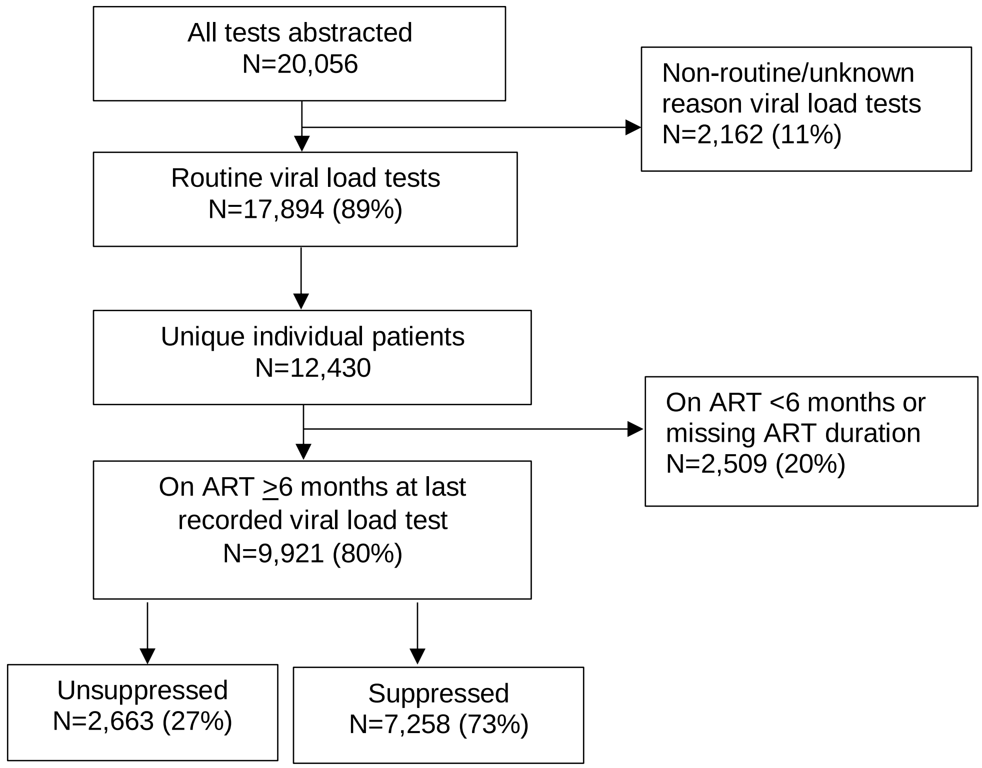


Table 1: Adolescent demographic characteristics at last viral load and clinic characteristics

	N	All N=9921	Suppressed N=7258 (73%)	Unsuppressed N=2663 (27%)
Adolescent characteristic		n(%)	n(%)	n(%)
Age-group	9921			
10-14		3397 (34%)	2284 (67%)	1113 (33%)
15-19		2315 (23%)	1572 (68%)	743 (32%)
20-24		4209 (43%)	3402 (81%)	807 (19%)
Sex	9885			
Male		3029 (31%)	1978 (65%)	1051 (35%)
Female		6856 (69%)	5251 (76%)	1605 (23%)
Mode of infection	9921			
Perinatal		4339 (44%)	2885 (67%)	1454 (34%)
Horizontal		5582 (56%)	4373 (78%)	1209 (22%)
ART Regimen	9871			
NNRTI		8866 (90%)	6496 (73%)	2370 (27%)
PI		891 (9%)	636 (71%)	255 (29%)
Other*		114 (1%)	85 (75%)	29 (25%)
ART duration	9921			
6months to 1 year		1560 (16%)	1266 (81%)	294 (19%)
1-2years		1923 (20%)	1519 (79%)	404 (21%)
2-5 years		3213 (32%)	2331 (73%)	882 (27%)
5-10 years		2684 (27%)	1769 (66%)	915 (34%)
Over 10 years		541 (5%)	373 (69%)	168 (31%)
Turn-around time	9896	12 (7, 19)	12 (7, 19)	12 (7, 21)
Clinic characteristics				
County HIV prevalence	**N =99**	**n(%), median (IQR)**		
Hyper endemic (>11.1%)		27 (26%)		
High (5-11.1%)		14 (14%)		
Medium (2-4.9%)		55 (56%)		
Low (<2%)		3 (3%)		
Clinic size & resources	99			
County		11 (11%)		
Sub-County		36 (36%)		
Health center/dispensary		50 (51%)		
Mission/Foundation		2 (2%)		
AYA in follow-up*	99	61 (36, 130)		
AYA:HCW ratio	99	6 (3, 10)		
Separate adolescent space	99	18 (18%)		
Nutritionist	99	60 (62%)		
Laboratory staff	99	74 (75%)		
Social worker	99	37 (37%)		
Community health worker	99	65 (66%)		
Adolescent services				
Adolescent days	99	90 (91%)		
Weekend	90	51 (57%)		
Snacks	90	12 (13%)		
More staff	90	15 (17%)		
Staff trained in APS	99	42 (43%)		
Using adolescent checklist	98	62 (63%)		
All day clinics	99	25 (25%)		
Can identify AYA records	99	74 (75%)		
Has mental health tool	92	72 (78%)		
Community activities				
School activities	99	42 (42%)		

Community activities	99	47 (47%	

*Integrase inhibitor, triple nucleotide, unspecified

p value <0.05 for age-group, sex, mode of infection and ART duration (except 1-2 years of ART)

Table 2: Individual and clinic level correlates of viral suppression

	Univariate		Model 1: Individual level		Model 2: Individual & clinic level	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Adolescent characteristics						
Age-group						
10-14	**0.50**	0.45, 0.55	**0.62**	0.55, 0.70	**0.62**	0.55, 0.71
15-19	**0.51**	0.45, 0.57	**0.59**	0.52, 0.67	**0.60**	0.52, 0.69
20-24	Ref		Ref	--	--	--
Sex						
Female	Ref	--	Ref	--	--	--
Male	**0.58**	0.53, 0.64	**0.72**	0.65, 0.80	**0.70**	0.63, 0.79
Mode of infection						
Horizontal	Ref	--				
Perinatal	**0.57**	0.52, 0.62				
ART Regimen						
NNRTI	Ref	--	Ref	--	--	--
PI	0.85	0.73, 1.00	1.03	0.88, 1.21	1.02	0.86, 1.21
ART duration						
6months to 1 year	Ref	--	Ref	--	--	--
1-2years	0.87	0.74, 1.03	0.90	0.76, 1.07	0.92	0.76, 1.11
2-5 years	**0.62**	0.53, 0.72	**0.67**	0.58, 0.79	**0.69**	0.58, 0.81
5-10 years	**0.46**	0.39, 0.53	**0.59**	0.50, 0.69	**0.59**	0.49, 0.70
Over 10 years	**0.53**	0.42, 0.67	**0.66**	0.52, 0.83	**0.69**	0.54, 0.89
Clinic characteristics						
County HIV prevalence						
Hyper endemic (>11.1%)	Ref	--			Ref	
High (5-11.1%)	0.87	0.68, 1.11			0.93	0.73, 1.20
Medium/Low (<4.9%)	**0.71**	0.60, 0.84			0.85	0.71, 1.02
Clinic size & resources						
County	Ref	--			Ref	
Sub-County	1.05	0.84, 1.32			0.96	0.74, 1.24
Health center/dispensary	**1.35**	1.08, 1.69			1.11	0.84, 1.51
Mission/Foundation	**1.95**	1.18, 3.21			**2.09**	1.35, 3.24
AYA in follow-up (per 100 AYA)	1.02	0.97, 1.07				
AYA:HCW ratio (10 unit increase)	1.05	0.96, 1.15			1.00	0.99, 1.01
Separate adolescent space	1.14	0.91, 1.43			**1.27**	**1.03, 1.56**
Nutritionist	0.90	0.76, 1.07			1.04	0.89, 1.22
Laboratory staff	0.94	0.78, 1.15			1.01	0.84, 1.08
Social worker	**0.79**	0.67, 0.93			**0.77**	0.66, 0.89
Community health worker	1.02	0.86, 1.22			0.94	0.79, 1.13
Adolescent services						
Adolescent days	1.16	0.82, 1.66				
Weekend	1.00	0.85, 1.18				
Snacks	1.04	0.82, 1.32			0.93	0.81, 1.08
More staff	0.96	0.76, 1.21			0.87	0.69, 1.09
Staff trained in APS	0.98	0.83, 1.16			0.88	0.72, 1.08
Using adolescent checklist	1.05	0.88, 1.25			0.98	0.82, 1.18
All day clinics	1.03	0.85, 1.25				
Can identify AYA records	1.00	0.82, 1.22			0.98	0.82, 1.18
Has mental health tool	1.08	0.86, 1.36			0.94	0.76, 1.15
Other activities						
School activities	1.11	0.93, 1.31			0.93	0.76, 1.15
Community activities	1.14	0.97, 1.34			1.12	0.94, 1.33
Turn-around time (10 day longer)	**0.95**	0.92, 0.97			**0.94**	0.92, 0.97

Mode of transmission, AYA in follow-up, model of care, weekend, add day clinics not included in model 1 or 2 due to collinearity

*Categories defined by Kenya Ministry of Health

Bolded: statistically significant, p values <0.05

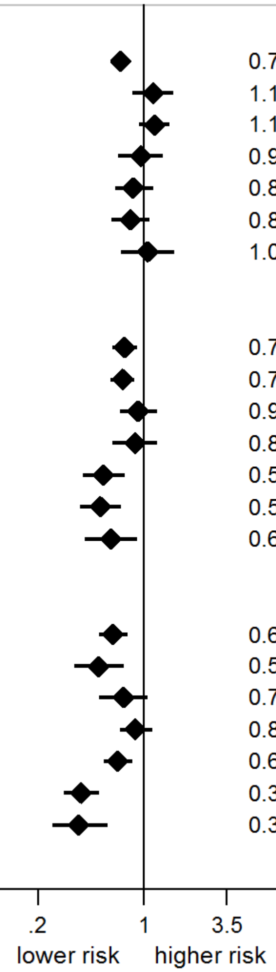
Table 2b: Summary of variance estimates and ICC

Model	**ICC**	**Interpretation of ICC**
Null model	0.029 (0.018, 0.457)	Proportion of variance explained by clinic
Model 1	0.025 (0.015, 0.041)	Unexplained variation explained by clinic
Model 2	0.005 (0.001, 0.022)	Unexplained variation explained by clinic

Figure 2: Individual level correlates of viral suppression stratified by age and sex

Panel A: By age-group

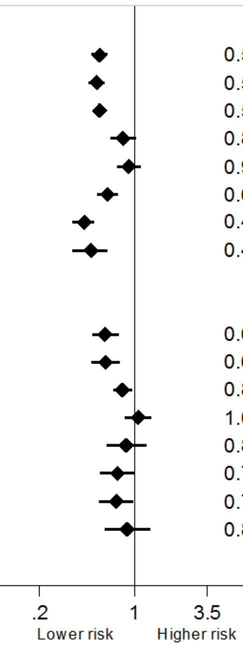
Age-group (N)	Correlates	N (n)	%	95% CI
10 to 14		**N=3397**		
	Males*	1619	48%	0.70 (0.60, 0.81)
	Perinatal^	3210	95%	1.15 (0.84, 1.57)
	PI-based^^	428	13%	1.17 (0.93, 1.47)
	ART 1-2yr**	393	12%	0.95 (0.67, 1.33)
	ART 2-5yr**	1100	32%	0.85 (0.64, 1.15)
	ART 5-10yr**	1446	43%	0.81 (0.61, 1.09)
	ART>10yr**	196	6%	1.06 (0.70, 1.60)
15 to 19		**N=2315**		
	Males*	867	38%	0.75 (0.62, 0.90)
	Perinatal^	987	43%	0.72 (0.60, 0.86)
	PI-based^^	278	12%	0.92 (0.69, 1.22)
	ART 1-2yr**	388	17%	0.87 (0.62, 1.23)
	ART 2-5yr**	640	28%	0.54 (0.40, 0.74)
	ART 5-10yr**	733	32%	0.52 (0.38, 0.70)
	ART>10yr**	215	9%	0.61 (0.41, 0.90)
20 to 24		**N=4209**		
	Males*	543	13%	0.63 (0.51, 0.78)
	Perinatal^	142	3%	0.50 (0.35, 0.73)
	PI-based^^	185	5%	0.73 (0.51, 1.05)
	ART 1-2yr**	1152	27%	0.88 (0.69, 1.13)
	ART 2-5yr**	1473	35%	0.67 (0.54, 0.84)
	ART 5-10yr**	504	12%	0.39 (0.30, 0.51)
	ART>10yr**	130	3%	0.37 (0.25, 0.57)



*compared to females
^compared to horizontal transmission
^^compared to NNRTI based ART
**compared to ART for 6-12 months

Panel B: By sex

Subgroup (N)	Correlates	N (n)	%	95% CI
Females		**N=6892**		
	Age 10-14*	1771	26%	0.56 (0.48, 0.64)
	Age 15-19*	1443	21%	0.53 (0.46, 0.61)
	Perinatal^	2272	33%	0.56 (0.50, 0.63)
	PI-based^^	461	7%	0.83 (0.67, 1.04)
	ART 1-2yr**	1507	22%	0.92 (0.75, 1.12)
	ART 2-5yr**	2253	33%	0.64 (0.53, 0.76)
	ART 5-10yr**	1528	22%	0.43 (0.35, 0.51)
	ART>10yr**	304	4%	0.48 (0.35, 0.64)
Males		**N=3021**		
	Age 10-14*	1619	53%	0.61 (0.49, 0.77)
	Age 15-19*	867	29%	0.62 (0.48, 0.79)
	Perinatal^	2060	68%	0.82 (0.70, 0.97)
	PI-based^^	429	14%	1.07 (0.85, 1.35)
	ART 1-2yr**	417	14%	0.88 (0.63, 1.24)
	ART 2-5yr**	951	31%	0.76 (0.56, 1.02)
	ART 5-10yr**	1149	38%	0.74 (0.55, 0.99)
	ART>10yr**	236	8%	0.89 (0.60, 1.32)



*compared to age 20-24
^compared to horizontal transmission
^^compared to NNRTI based ART
**compared to ART for 6-12 months

Table 3: Clinic characteristics stratified by overall clinic viral suppression status

Clinic characteristic	All N=99 n(%) /Median (IQR)	% suppressed in clinic >=80% N=14 n(%) /Median (IQR)	70-80% N=48 n(%)/Median (IQR)	<70% N=25 n(%)/Median (IQR)
County HIV prevalence				
Hyper endemic	27 (26%)	**7 (50%)**	**16 (33%)**	**4 (11%)**
High	14 (14%)	**2 (14%)**	**8 (17%)**	**4 (11%)**
Medium	55 (56%)	**5 (36%)**	**23 (48%)**	**27 (73%)**
Low	3 (3%)	**0**	**1 (2%)**	**2 (5%)**
Clinic size & resources				
County	11 (11%)	**0**	**5 (10%)**	**6 (16%)**
Sub-County	36 (36%)	**2 (14%)**	**15 (31%)**	**19 (51%)**
Health center/dispensary	50 (51%)	**11 (79%)**	**27 (56%)**	**12 (32%)**
Mission/Foundation	2 (2%)	**1 (7%)**	**1 (2%)**	**0**
AYA in follow-up*	61 (36, 130)	58 (33, 101)	69 (41, 178)	48 (30, 111)
AYA:HCW ratio	6 (3, 10)	5 (2, 12)	7 (3, 11)	6 (3, 7)
Separate adolescent space	18 (18%)	5 (36%)	7 (15%)	6 (16%)
Staffing in HIV clinic				
Nutritionist	60 (61%)	7 (50%)	28 (58%)	25 (68%)
Laboratory staff	74 (75%)	10 (71%)	37 (77%)	27 (73%)
Social worker	37 (37%)	**1 (7%)**	**18 (38%)**	**18 (49%)**
Community health worker	65 (66%)	10 (71%)	34 (71%)	21 (57%)
Adolescent services				
Model of care				
Adolescent days	90 (91%)	12 (86%)	46 (96%)	32 (87%)
Weekend	51 (57%)	5 (42%)	30 (65%)	16 (50%)
Snacks	12 (13%)	3 (25%)	4 (9%)	5 (16%)
More staff	15 (17%)	3 (25%)	5 (11%)	7 (23%)
Staff trained in APS	42 (43%)	5 (36%)	22 (46%)	15 (42%)
Using adolescent checklist	62 (63%)	9 (64%)	33 (70%)	20 (54%)
All day clinics	24 (24%)	12 (86%)	34 (71%)	28 (76%)
Can identify AYA records	74 (75%)	10 (71%)	36 (75%)	28 (76%)
Can screen mental health	72 (78%)	11 (85%)	36 (80%)	25 (74%)
Community activities				
School activities	42 (42%)	8 (57%)	21 (44%)	13 (35%)
Community activities	47 (47%)	8 (57%)	24 (50%)	15 (41%)
Group summary variables				
Viral load turnaround time (days)	12 (9, 14)	**8 (6, 11)**	**12 (10, 14)**	**11 (8, 13)**

*Numbers generated from abstracted medical record
Bolded: statistically different (p<0.05)

CHAPTER 3A: What happens at adolescent and young adult HIV clinics? A national survey of models of care, transition, and disclosure practices in Kenya

ABSTRACT

Introduction: Tailored services for adolescents and young adults (AYA) living with HIV may improve treatment outcomes. We surveyed HIV clinics throughout Kenya to determine AYA clinic practices, disclosure and transition services.

Methods: We deployed a mobile team to conduct surveys in a random sample of 102 public HIV clinics with >300 clients. Data was collected from health care workers offering AYA services who had ≥6 months experience delivering AYA care prior to the interview.

Results: Of 102 surveyed HIV clinics, almost all (101/102) had the same staff provide services to all age groups. Alternative structures supported AYA specific services including dedicated clinic days (91%), the majority being on weekends (57%) and designated clinic spaces (20%).

Activities to support AYA retention and adherence were common (support groups [97%] and HIV literacy meetings [93%]). Fewer clinics offered more holistic care including psychosocial support (16%) and career education (2%), posted additional staff during the AYA day (17%), provided food (17%) or had sporting activities (10%) as incentives.

Tracking of disclosure of HIV status to AYA was common (87%). In 40% of clinics, there was a median 2 year policy to practice delay in initiating disclosure discussions with caregivers or AYA.

Transition was not routinely tracked, and definitions were heterogeneous. Median age at transition was reported as 20 years (range:14-30 years).

Conclusion: HIV programs have implemented varied approaches to enhance AYA services that could be leveraged to support transition to adult services. Research on the impact of these services on health outcomes is needed.

INTRODUCTION

Adolescents and young adults (AYA) living with HIV are a high priority population for poor outcomes. Poor adherence and unsuppressed viral loads[58,95,96], high rates of mortality[22], and loss to follow-up[97,98] remain highest in AYA compared to other age groups. Loss to follow-up is particularly high among 15-24 year olds[97,98], an age group that experiences health care transition to adult services. Supporting AYA during the vulnerable period of transition is crucial to optimizing health outcomes.

Despite being a critical process, transition from pediatric to adult HIV services in sub-Saharan Africa (SSA) is poorly defined and unstructured[24]. Data on transition services for chronic non-infectious diseases is similarly lacking in this setting, making it difficult to adapt transition practices for AYA living with HIV. In resource rich countries, transition programs have been developed for HIV[99] and chronic non-infectious diseases[100-103]. In these settings, structured transition programs are associated with improved clinical outcomes[104,105]. These programs are often multidisciplinary, individually tailored, and support AYA to gain the knowledge and skills they need in adult care systems. Toolkits to support development of transition programs are also available[106,107]. Key elements considered in these toolkits include defining transition policies, developing systems for individual tracking and monitoring, assessing readiness to transition, planning transition and actual transfer, and monitoring outcomes post-transition[108,109].

There are limited data on current transition practices in SSA[24,25]. Adolescent friendly services are recommended[110], but clinic practices vary[24]. Practices and tools around disclosure of HIV status to adolescents, a prerequisite to transition, are also poorly described. Late age at disclosure, partly due to lack of health care worker (HCW) guidelines and tools to support disclosure, are common challenges[111-113]. Tools for disclosure are available[64] but may be underutilized.

The Kenyan Ministry of Health (MoH) introduced the adolescent package of care (APOC) in 2015[76]. This package includes HCW training on AYA services and a checklist to prompt and capture services offered. The checklist includes assessment of BMI, Tanner staging, disclosure, adherence to medication, mental status, school attendance, participation in support groups, transition preparation, and for AYA girls, pregnancy testing, contraception, and HPV vaccination. Use of the checklist may be associated with improved viral suppression and better uptake of family planning services among AYA age 10-19[77]. While the checklist reminds health workers to prepare AYA for transition, and a job aid with a transition algorithm for guidance on age-based transition milestones is available, consensus national definitions of transition, measures of successful transition, and tools to individual track progress are lacking. With the growing population of perinatally infected children aging into adolescence and high numbers of newly infected AYA in SSA, there is need to better understand current AYA services, models of care and disclosure and transition practices in order to build effective support strategies.

This study aimed to characterize AYA services, HIV disclosure, and transition services in a sample of 102 HIV clinics providing services to AYA ages 10-24 years in Kenya.

METHODS

Study design and setting

This was a cross-sectional study conducted as part of pre-trial clinic assessments to understand transition practices in Kenya in the Adolescent Transition to Adult care for HIV infected adolescents (ATTACH) study (NCT03574129). This is a cluster randomized controlled trial (RCT) aimed at testing the effectiveness of an adolescent transition package to improve rates of disclosure, and transition readiness and success among HIV positive AYA in Kenya.

Site selection

Among 590 HIV clinics that had >300 individuals in HIV care and had electronic medical records (EMRs) in 2016, 102 clinics were randomly selected (Figure 1). The 590 clinics that met inclusion criteria were divided into tertiles based on the total number of adults ever enrolled and 34 clinics were randomly selected from each tertile, allowing equal representation of clinics with different patient volumes. Inclusion of clinics with more than 300 clients was based on an assumption that 10% of the population would be AYA (age 10-19), therefore, it was expected that each surveyed clinic would have at least 30 AYA.

Ethical considerations

The study received approval from the University of Washington (UW) Institutional Review Board (IRB) and the Kenyatta National Hospital (KNH) University of Nairobi (UoN) Ethical Review Committee (ERC). In addition, the study received approval from the Kenya Ministry of Health National AIDS and STI Control Program (NASCOP), County departments of Health in counties of participating clinics, and clinic managers.

Data collection and analysis

Data collection began in December 2017 and was completed in January 2019. Survey respondents were HCWs age $\geq$18 years, currently working with AYA in the HIV clinic, and had worked in the clinic for at least 6 months. Written informed consent was obtained in-person and surveys were conducted in-person or by phone. The questionnaire included questions on clinic characteristics including: AYA services, models of care and disclosure and transition services. Respondents completed the paper-based questionnaire prior to the interview, and then reviewed responses with study staff during the interview. Data was then entered into a REDCap[78] database. We used descriptive statistics to describe clinic characteristics, models of care and disclosure and transition services and chi2 test and t-test to compares clinic practices. All data analysis was done using STATA version 14.

RESULTS

The 102 selected clinics were in 27 of the 47 counties in Kenya. The majority of staff interviewed were clinical officers (59%) or nurses (25%). The median duration they had worked in AYA HIV care and time in current clinic were 32.5 (interquartile range [IQR]: 17, 48) and 24.5 months (IQR: 15, 41), respectively.

Clinic demographics: clinic volume and staffing

The majority of the HIV clinics (51) were in health centers or dispensaries, 12 were in County hospitals, 37 were in sub-County hospitals and 1 each were mission and foundation hospitals. Overall, clinics served a median of 51 (IQR: 34, 115) AYA.

Patient volume differed with clinic type, with HIV clinics in County and mission/foundation hospitals serving the largest number of AYA (260 [IQR: 120, 365] and 290 [IQR: 182, 398], respectively), while those in sub-County hospitals and health centers/dispensaries serving over 4 times fewer AYA (59 [IQR: 38, 115] and 44 [IQR: 28, 68], respectively) (Table 1). Overall, AYA comprised 12% of the total clinic population.

Despite higher total client volumes, clinics in larger hospitals (County/mission/foundation) served a lower proportion of AYA (13% vs 12%, $p<0.001$) compared to smaller clinics, and had significantly lower staff to AYA ratios compared to smaller clinics (1:4 vs 1:11, $p<0.001$ in HIV clinics in county hospitals) and (1:7 vs 1:11, $p<0.001$ in clinics in mission/foundation hospitals).

AYA services

It was rare to have staff that specialized solely on AYA-specific care. Only seven clinics had specific staff who were designated to work in the AYA clinic, however, these same staff also provided care for adults in six of the seven clinics. Clinic staff was weighted more towards general medical care and general counseling, with few psychosocial specialists and few high cadre medical specialists. Almost all clinics (98%) had a clinical officer (equivalent to physician assistants in the USA). The majority had counselors (85%), nurses/nurse counselors (80%), peer educators (89%) and laboratory technicians (74%). Almost two-thirds had community health workers (65%), or nutritionists (62%) and about over a third had social workers (38%). Only 10% of clinics had psychologists or psychiatrists, and fewer (8%) had medical doctors (Table 1).

While AYA-specific staffing was uncommon, designating specific times and spaces to AYA-specific care was relatively common. Almost all clinics (91%) had a separate day or days dedicated to AYA services. In 57% of those clinics the AYA day was on a weekend (Saturday/Sunday). Only 20% had a separate space in the clinic where AYA services were provided (Table 1). AYA services were provided all day in the majority of clinics (74%),and did not differ by whether clinics had AYA-specific days (73% in those with AYA-days and 89% in those without, p=0.30). Clinics in smaller hospitals were as likely to have weekend clinic days (36% vs 55% p=0.19) and separate space (20% vs 7%, p=0.235) as larger clinics.

During AYA-specific days, it was common for AYA to have access to supportive services aimed primarily at treatment adherence. A majority of clinics with an AYA-specific days also held support groups or teen clubs (97%) and treatment literacy meetings (93%) on the dedicated AYA clinic day, and 15% preferentially posted staff with AYA training to the clinic. Other activities/support included snacks/lunch (13%), games (10%), psychosocial support (16%) or career education (2%). Seventeen percent of clinics had additional staff on the AYA day to support additional services; the majority peer educators or adolescent champions (71%). Other staff who specially attended the AYA-specific days included program officers, counselors, psychologists, religious leaders or children officers.

Scheduling AYA visits was generally tailored towards supporting them to receive AYA-specific services and to meet their clinical needs. Clinical officers who largely provided medical care were also responsible for scheduling AYA visits in 83% of clinics. Medication adherence (91%) and poor clinical condition (49%) where commonly considered when deciding clinic visit frequency. AYA faring poorly were given shorter intervals between visits. Visit scheduling also took into account the availability of the AYA (81%), availability of the caregiver (23%), or whether the clinic was overbooked (12%). Almost all (94%) clinics with an AYA clinic day informed AYA that they were scheduled to attend clinic on the AYA day.

In recognition of the unique AYA needs and risk of poor outcomes, majority of clinics defined adolescents largely by WHO guidelines (age 10 [78%] to age 19 [72%]), 69% of clinics had started using the Kenyan MoH adolescent package of services including the adolescent checklist (62%), and had developed systems to uniquely identify AYA records (74%).

Disclosure and transition services

Most clinics (89%) had age-based policies for when health care providers should begin disclosure discussions with caregivers and children. However, there was a gap between policy and practice regarding the age to initiate disclosure discussions. Almost half (44%) of the clinics reported that disclosure discussions with caregivers began in practice at a median of 2 years (IQR: 2, 4) later than the clinic policy-recommended ages. Similar gaps existed with age to begin disclosure discussions with children. Forty-six clinics reported a median delay of 2 years (IQR: 2, 4) between policy-recommended ages for initiation and disclosure discussion initiation with children in practice (Figure 2). The median typical age at full disclosure was reported by HCW to occur at 12 years (IQR: 10, 15) (Figure 3).

Age was an important component of defining when transition began and completed. Almost all clinics (93%) had policies that specified age at which transition discussions should begin and end (94%), despite heterogenous transition definitions. By policy, median age at start of discussions was 18 years (IQR: 15-19) and completion of transition was 20 years (IQR: 19-24). Transition typically occurred at age 21 (IQR: 19-24) with peaks at age 20 and 24 (Figure 3). In the majority (78%) of clinics, transition was defined by an AYA demonstrating independence in their own care. Other definitions included: reaching a certain age (58%), independently collecting antiretroviral medication (49%), completing an adult clinic visit (27%), completing a formal transition process (25%), becoming pregnant (5%), and switching to adult ART regimens (1%).

Where policies were available, national guidelines were most commonly used; with disclosure guidelines more commonly used than transition guidelines (97% and 67%, respectively). The MoH adolescent checklist was commonly used to track disclosure (67%) and transition (41%). While clinics using the checklist reported to achieve full disclosure slightly earlier (12 years [IQR: 10-15]) compared to those not using (12.5 years [IQR: 12-15]), the difference was not significant (t-test p=0.15). A few clinics used additional tools like disclosure and transition readiness assessment checklists (42% and 19%, respectively) (Table 2). Many staff cadres were involved in initiating disclosure and transition discussions. Disclosure discussions were typically initiated by clinical officers (78%), counselors (63%), nurses (52%), caregivers (58%), and peer educators (50%) while transition discussions were typically initiated by clinical officers (88%), nurses (60%), counselors (58%), and peer educators (51%). Only 52% of clinic documented the transfer to adult services and 66% tracked AYA post-transfer to adult clinics.

DISCUSSION

In this national survey of 102 clinics in Kenya, we found that HIV clinics had adopted models of care to address unique AYA needs. Despite largely utilizing the same clinic staff and space for all HIV positive clients, specific AYA focused activities, including AYA clinic days, flexible scheduling and weekend clinics were common. While national guidelines offered guidance for disclosure and transition, there were delays in offering disclosure services and transition guidelines were less commonly used. Clinics had a way of defining transition, relying mostly on age, though the definitions were heterogenous. Individualized transition tracking, readiness assessment, planning and monitoring outcomes was uncommon, and use of disclosure and transition tools beyond those in the national guidelines were rare.

Our findings on the models of AYA care reflect those of other settings in SSA, where AYA clinic days are common, with the same staff caring for all age groups[24,25]. In a survey of Nigerian HIV clinics in 2016, only 28% of clinics had an AYA clinic day, which is substantially lower than in Kenya and could be explained by growing interest and focus for AYA friendly services in Kenya[76]. While AYA clinic days help to focus AYA services, there is evidence of poor utilization of particularly non clinical services with only a third of Ugandan AYA regularly utilizing the clinics and services offered [74]. This could be a result of conflicting school or work schedules. Indeed, a majority of surveyed clinics reported AYA availability as the most important consideration during scheduling. Understanding barriers to attending AYA clinic days and outcomes of AYA who do not utilize them may important in developing approaches that meet the needs of all AYA. We found that clinical officers who primarily provided medical care, also provided disclosure and transition services in almost all clinics. The median number of clinical officers was 1 per clinic, therefore, task shifting for disclosure and transition services may be beneficial. We noted very few mental health experts – only 10% of clinics had access to a psychologist or psychiatrist despite well described mental health challenges in AYA[19].

Late age at disclosure is common in SSA[114]. We found that the majority of clinics typically reached full disclosure by age 10-15 which is later than the national target of full disclosure by age 9-12[80]. Inclusion of disclosure guidelines in national HIV guidelines and expanding the use of APOC may improve age at disclosure[80,115]. While many clinics had disclosure policies, we found a lag in actual practice, with full disclosure typically occurring much later than recommended by clinic policies and national guidelines[80]. Caregiver support for disclosure or task shifting in addition to child friendly tools to support disclosure may promote early disclosure. Standard toolkits proven to improve outcomes[64]may provide a more comprehensive approach to disclosure.

As in many SSA settings, transition definitions were heterogeneous[25]. There was little time between the typical age at initiation of transition discussion and age at transition, and this may contribute to AYA discomfort in adult services [116]. The goal of transition is to support AYA to gain life-skills and knowledge to independently manage their care[117] which could be viewed as a process. Implementing transition services at an earlier age and within existing support services outside clinic services such as during support groups or treatment education meetings already implemented in majority of clinics may be a feasible approach. Task-shifting transition roles may be useful if clinic volumes are high or depending on staffing configurations.

While the Kenya MoH APOC[115] checklist provides a cue to remind health care workers to initiate discussions on transition, only one question “Has transition preparation discussion began (yes/no)” is dedicated to transition and one to disclosure “Disclosure done (partial/full)”. These questions are limited, and do not provide tracking of components within the process of transition and disclosure. The WHO and chronic non-infectious literature defines transition as ‘gaining knowledge and skills to independently manage care[100,117]’, which would be difficult to assess with this tool. However, the APOC tool is an excellent start, as it provides a foundation that can be expanded to capture transition goal. It is widely used in AYA clinics, and its use has been associated with improved viral suppression[118].

Our study is timely with data collected up to the end of 2018. However, AYA clinic practice are dynamic and are likely to continue to evolve in the coming years. We sampled clinics based on clinic volume and use of electronic medical records. These clinics may more likely be better resourced and may not generalize to the whole country. Our results may provide important current evidence of AYA models of care, and disclosure and transition practices in clinics in program settings in Kenya. A strength of our study was that clinics were selected from a nationally representative sample which include clinics in over half of the counties in Kenya.

In conclusion, HIV care programs in SSA have implemented a variety of innovative approaches to address unique AYA needs, however, there is limited evidence regarding the impact of these diverse models. It will be important to understand ideal models of AYA care that result in improved outcomes and the impact of these models, particularly those with incentives on post-transition outcomes. There is promising progress in implementing tools to capture disclosure and transition practices, however, lack of standard transition definitions, and inadequate information on tracking tools make it challenging to evaluate transition. Research to close the policy-practice gap for disclosure, develop consistent transition definitions, tracking and monitoring systems is urgently needed.

TABLES AND FIGURES

Figure 1: Distribution of study sites and County HIV prevalence

Adapted from the Kenya HIV estimates report 2018. Available at: https://nacc.or.ke/wp-content/uploads/2018/11/HIV-estimates-report-Kenya-20182.pdf

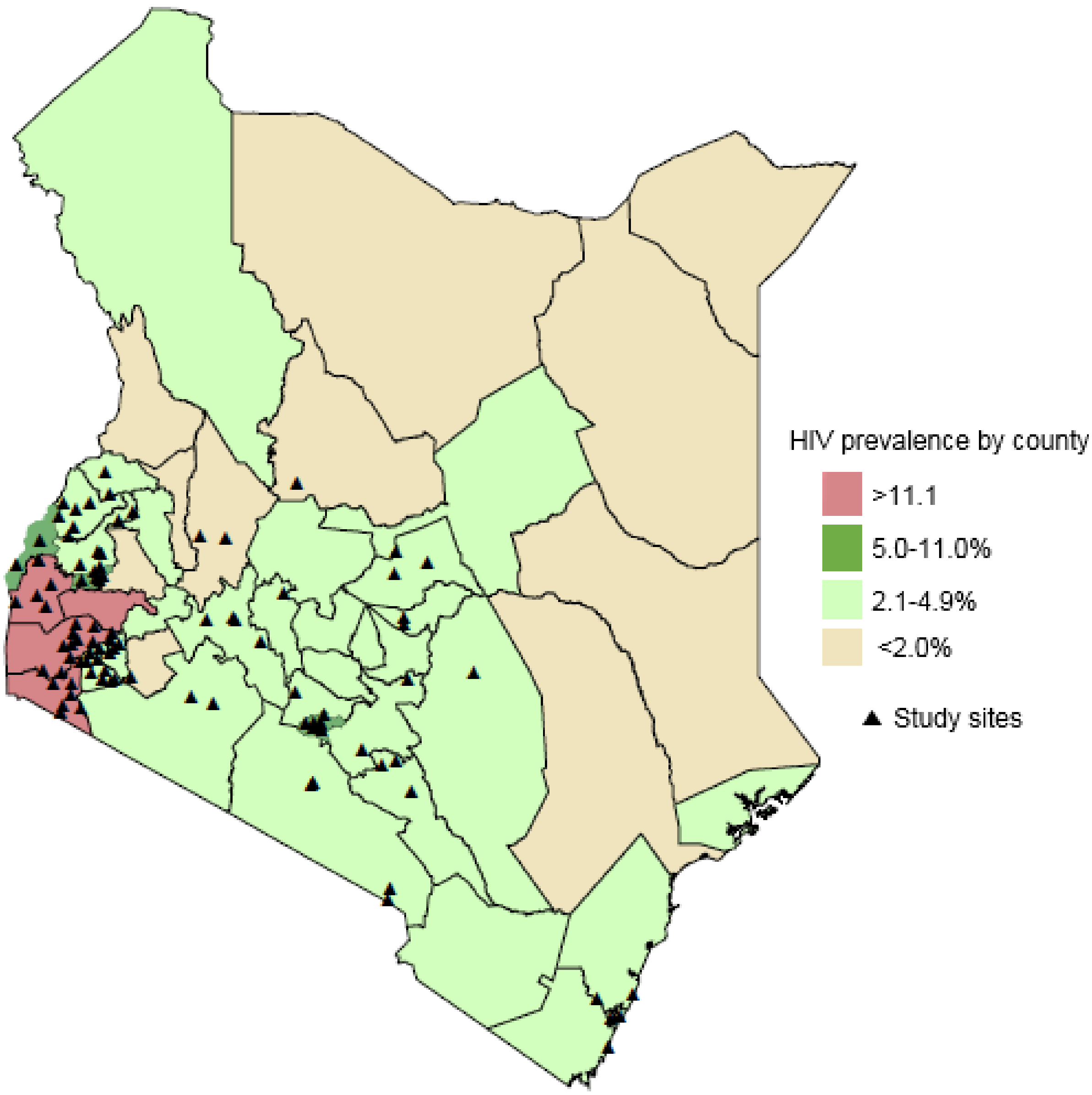


Table 1: Clinic characteristics and AYA services available

Clinic characteristics (N=102)	n(%) / median (IQR)
Facility characteristics	
Facility type	
County	12 (12)
Sub-County	37 (36)
Health center/dispensary	51 (50)
Mission/Foundation	2 (2)
AYA in active follow-up (N=90)	51 (34, 115)
County	260 (120, 365)
Sub-County	59 (38, 115)
Health center/dispensary	44 (28, 68)
Mission/Foundation	290 (182, 398)
Staffing	
Number of staff at HIV clinic	15 (10, 21)
County	19 (16, 23)
Sub-County	15 (11, 20)
Health Center/dispensary	12 (9, 19)
Mission/Foundation	40 (24, 55)
Has specific staff for AYA clinic	7 (7)
Has staff who see only children or AYA	1 (1)
Staff type for HIV clinic	
Clinical officers	100 (98)
Counselors	87 (85)
Nurses/Nurse counselors	82 (80)
Peer educator	91 (89)
Laboratory technician	75 (74)
Nutritionists	63 (62)
Social workers	39 (38)
Community health workers	66 (65)
Psychologists/Psychiatrists	10 (10)
Medical officers	8 (8)
Clinic model of care	
AYAday	93 (91)
Weekend AYA day	53 (57)
In separate AYA clinic	19 (20)
Integrated clinic	9 (9)
Definition of adolescent	
Lower limit 10 years of age	79 (77)
Upper limit 19 years of age	73 (72)
AYA records	
Has method to identify records	75 (74)
Sticker	22 (29)
Folder color or tag	30 (40)
Filing system	16 (21)
Identification numbers	4 (5)
Electronic medical records	3 (4)

Table 2: Disclosure and transition services

Disclosure and transition services N=102	n(%) / median (IQR)
Disclosure	
Has disclosure guidelines	99 (97)
National guidelines	96 (97)
Has disclosure tools	87 (85)
MoH adolescent checklist	68 (67)
Tracks individual disclosure start	93 (91)
Tracks individual disclosure status	89 (87)
Transition	
Clinic definition of transition	
Shows independence in their own care	80 (78)
Specific age	59 (58)
Picks medication on their own	50 (49)
Has attended adult clinic	26 (26)
Completion of a formal transition ceremony	25 (25)
Becomes pregnant	5 (5)
Switch from pediatric to adult ART regimen	1 (1)
Has transition guidelines	70 (69)
National guidelines	67 (97)
Has transition tools	50 (49)
MoH adolescent checklist	42 (84)
Readiness assessment tools	19 (38)
Other transition tools	15 (30)
Tracks transition completion	61 (60)
Documents transfer to adult services	53 (52)
Tracks AYA post-transfer	67 (66)

Figure 2: Practice policy gap in age to begin caregiver and child disclosure discussions

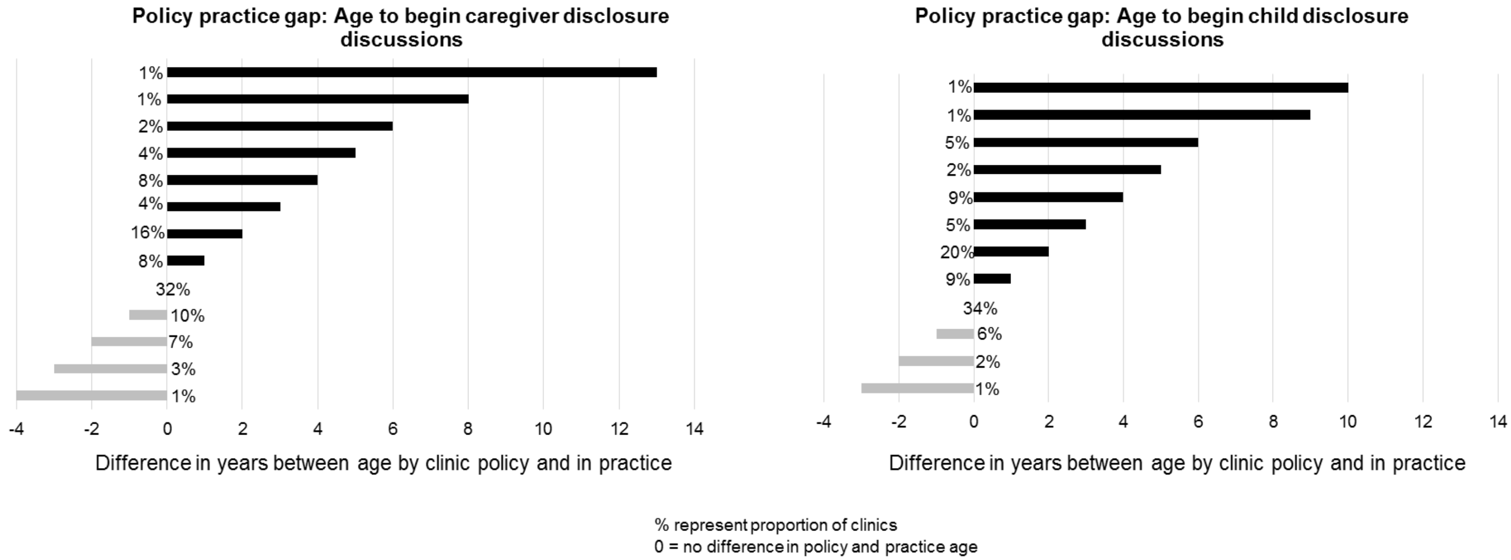
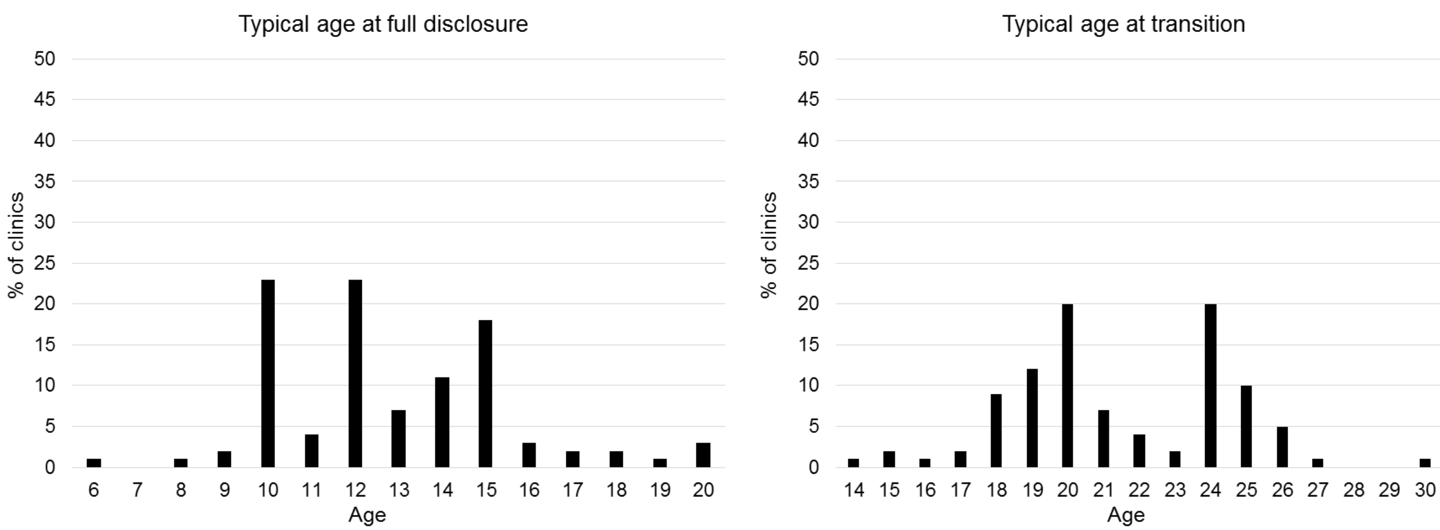


Figure 3: Typical age at full disclosure and transition



CHAPTER 3B: Transition from pediatric to adult HIV care: Consensus definition and key elements in programmatic settings in sub-Saharan Africa

ABSTRACT

Introduction: Establishing formalized processes can support adolescents living with HIV (ALWHIV) to successfully transition from pediatric to adult care. In sub-Saharan Africa (SSA), transition processes remains poorly defined and unstructured, which may jeopardize treatment adherence and retention in care. Our objective was to develop a consensus definition of transition among Kenyan stakeholders for use in HIV treatment programs.

Methods: Purposively selected stakeholders in Kenya reviewed World Health Organization definitions of transition, definitions of transition from existing tools used in HIV and other chronic diseases, and current transition practices in HIV clinics in Kenya.

Results: Among 32 stakeholders, the consensus definition of transition was "*a planned process by which ALWHIV, and their caregivers, are empowered with knowledge and skills to enable them to independently manage their health*". Participants felt that the transition process should begin soon after disclosure of HIV status and continue until the adolescents gained necessary knowledge and skills and were *ready* and *willing* to move to adult services. Transition to adult care was expected to be completed by 25 years. Key elements of transition included: identification of target ages for milestone achievement, readiness assessment, caregiver involvement, communication with adult clinic, flexibility to return to adolescent clinics, group transition where possible, and considerations for adolescents with special needs. Participants identified retention, linkage to care and viral suppression as the most important markers of transition success.

Conclusion: We identified transition definitions, key elements and markers of successful transition that could provide a framework for structuring transition programs in sub-Saharan Africa (SSA).

INTRODUCTION

HIV-associated mortality among adolescents ages 15-19 remains high,[22] adherence to medication is sub-optimal,[96] and loss to follow-up among 15-24 year-olds is twice as high as that of younger adolescents (10-14 years) or adults (≥24 years).[97] Transition from pediatric or adolescent HIV care to adult services is emerging as a critical step for maintaining good outcomes among adolescents and young adults living with HIV (ALWHIV). As adolescents transition into adulthood, they must acquire knowledge and skills to independently manage their care. However, the adolescent period is marked by physical, cognitive, and social changes that coincide with other changes in life that could contribute to challenges in HIV management seen in ALWHIV.

Structured transition programs can support ALWHIV to develop the knowledge and skills they need for successful transition into adulthood. In developed countries, a physical transition from pediatric to adult care is common, and transitional models of care are available.[100,101,103] The lack of structured transition programs in sub-Saharan Africa (SSA) reflects a broader gap in bridging pediatric-adolescent-adult oriented services for chronic illness in general, and for HIV specifically.[119]

Clinics in SSA have a range of models of care for adolescents; the majority provide care in clinics where adults, adolescents and children living with HIV are seen by the same staff in the same place.[25,119] However, “adolescent friendly services”, usually in the form of a dedicated adolescent clinic day, are increasingly implemented.[25,119] Definitions and tracking systems for transition are relatively new and varied [25] and transition focused services are short-lived, typically occurring in the context of research projects.[24] In programmatic settings across SSA, age is commonly used to define transition, with age 18 being most common, although a wide range exists (12-24).[25,119] Other transition defining events include demonstrating independence by coming to clinic alone, independently picking up medication, marriage and pregnancy[25]. Existing transition frameworks used in developed countries could be adapted for use in resource limited settings.

METHODS AND RESULTS

We conducted a workshop aimed at adapting and optimizing an Adolescent Transition Package (ATP) for Kenyan HIV clinics. This work was conducted as part of the Adolescent Transition To Adult HIV Care for HIV-infected adolescents in Kenya (ATTACH) study (NCT03574129) which aims to develop and test an ATP to support adolescent transition to independent care.

The workshop was conducted in September 17-18, 2018, and included 32 key stakeholders purposively selected from a broad range of HIV care leaders including the Kenya Ministry of Health, county leads, implementing partners, mental health experts, healthcare providers from pediatric and adult settings, and adolescent representatives. Selection was designed to provide broad representation, including from high HIV prevalence regions in Western Kenya and a mix of rural and urban settings. The agenda for the workshop was prepared collaboratively by the study team and the Ministry of Health. The 2 day workshop focused on 4 key areas that mirror critical processes in transition: 1) transition definitions, 2) transition tracking, 3) readiness assessment, and 4) post-transition monitoring. Two non-study team leaders were pre-selected per transition area to facilitate small group discussions. All groups discussed transition definitions in small groups and in a plenary session on day 1 of the workshop. On day 2, a smaller transition definitions group synthesized information presented and discussed on day 1 (Figure 1). Summaries of discussions were entered into pre-prepared worksheets.

Summaries of existing transition definitions and tools for tracking, monitoring and readiness assessment were shared with team leaders prior to the workshop and with participants during the workshop. Specific to transition definitions, the following materials were shared: WHO definitions of transition, definitions from existing transition tools, definitions from chronic non-infectious disease literature, definitions from HIV literature, data on current transition definitions in 55 large HIV clinics and qualitative interviews with healthcare workers.

This paper focuses on deliberations on the following key concepts: 1) national definition for transition, 2) key elements of transition, and 3) defining successful transition.

Transition definition

The group defined transition as **"a planned process by which HIV-infected adolescents and young adults, and their caregivers, are empowered with knowledge and skills to enable them independently manage their health".** Transition was viewed as a process that begins soon after disclosure of HIV status, and continues until the adolescent gains the knowledge and skills they need, and is *ready* and *willing,* to move to adult oriented services. Key elements of transition included identification of target ages for milestone achievement, readiness assessment, caregiver involvement, communication with adult clinic, flexibility to return to adolescent clinics, group transition where possible, and special considerations for adolescents with special needs (Table 1).

While age was considered an important indicator to guide transition milestones, participants noted the importance of considering developmental age and emotional readiness. Transition discussions were proposed to begin as early as possible after disclosure of HIV status, and by age 14. Adolescents were expected to have fully transitioned by age 25, but dependent on each adolescent's unique development. Readiness to transition would be assessed before transfer to adult care or adult models of care, and should include adolescent's assessment of their own willingness to transition. This assessment would review: treatment literacy, communication skills, life transitions including school and work transition, being on an optimized antiretroviral (ARV) regimen, and being clinically stable (virally suppressed, no active opportunistic infection). The caregiver was identified as critical to the process and should be empowered to support treatment literacy and enable adolescents to build independence (Table 1).

In clinic settings where adolescent and adult services were offered separately, communication between providers was identified as important to facilitate a smooth transition. Participants described the idea of "young adult clinics" within adult clinics where young adults (ages 18-24) would attend clinic on a specific day as well as flexibility to attend either adult or adolescent clinics as they felt comfortable. Group transition, (referring to transition of cohorts who have been in care together) when possible, and transition support groups composed of recently transitioned adolescents, were identified as ways to facilitate more formal support and improve successful transition.

Successful transition

Successful transition was defined as: 1) ≥1 clinic visit within 3 months of their last clinic visit in an adolescent/pediatric care system (linkage), 2) ≥3 visits over a 12-month period (retention) and 3) consistent viral load measurements below the level of detection for ≥12 months (viral suppression). Post-transition follow-up should include contact at 3 months to evaluate linkage and at 6-12 month to assess retention, viral suppression, and experiences in adult care.

The consensus definition of transition aligned with the WHO definition of "planned purposeful movement of adolescents from pediatric focused models of care to adult care whose goal is to support the adolescent to become autonomous in their own care". The emphasis on gaining knowledge and skills to navigate adult oriented services, borrowed from non-infectious disease literature, is an important component of transition. Demonstrating appropriate knowledge and skills, and expressing willingness to take responsibility for care, were thought to be important precursors for independence. This definition would apply to all available models of adolescent care in Kenya, whether there was an actual patient transfer of services or care was continued by the same clinician or within the same clinic space.

DISCUSSION

Transition was defined as a process rather than an event, with need to begin early. Transition practices in programs where actual transfer occurs are designed largely to support transfer to adult services, with preparation beginning close to the physical transfer to adult services. The age at which transition discussions should begin was thought to be much earlier than previously documented in literature from developed countries[99] which may allow the desired psychological preparation prior to transition.[116,120] Beginning transition preparation earlier in SSA may be beneficial, as adolescents often present to clinic alone due to challenges with transportation costs, orphan hood, caregiver illness, and lack of disclosure to others.[121]

Rather than relying on age alone, workshop attendees advocated for a multi-component assessment of transition readiness, based on gaining minimum HIV literacy, communication skills, self-management skills and a support system required for adult care and expressing willingness to transition. Within resource-limited settings, perinatal HIV, social environment, including poverty, nutritional deprivation and challenging support systems due to inconsistent caregivers, may influence neurodevelopment and therefore transition readiness particularly among HIV-infected orphaned and vulnerable children. However, tools to assess developmental maturity, largely left to clinician judgement, are lacking and warrant further investigation.

While the transition definitions workshop was conducted in Kenya, findings could be translated to SSA settings with similar models of care. While identifying a practical way to track and assess transition in program settings remains challenging, this data provides a framework for better understanding transition definitions and processes in SSA and can support the development of interventions to improve transition outcomes.

A clear definition of transition and key elements of the transition process for ALWHIV in SSA may support clinics to develop structured transition programs. The transition definition and process milestones identified during the workshop will be used to develop transition tools and support tracking of transition outcomes in HIV programs in Kenya.

TABLES AND FIGURES

Figure 1: Organization of the transition workshop

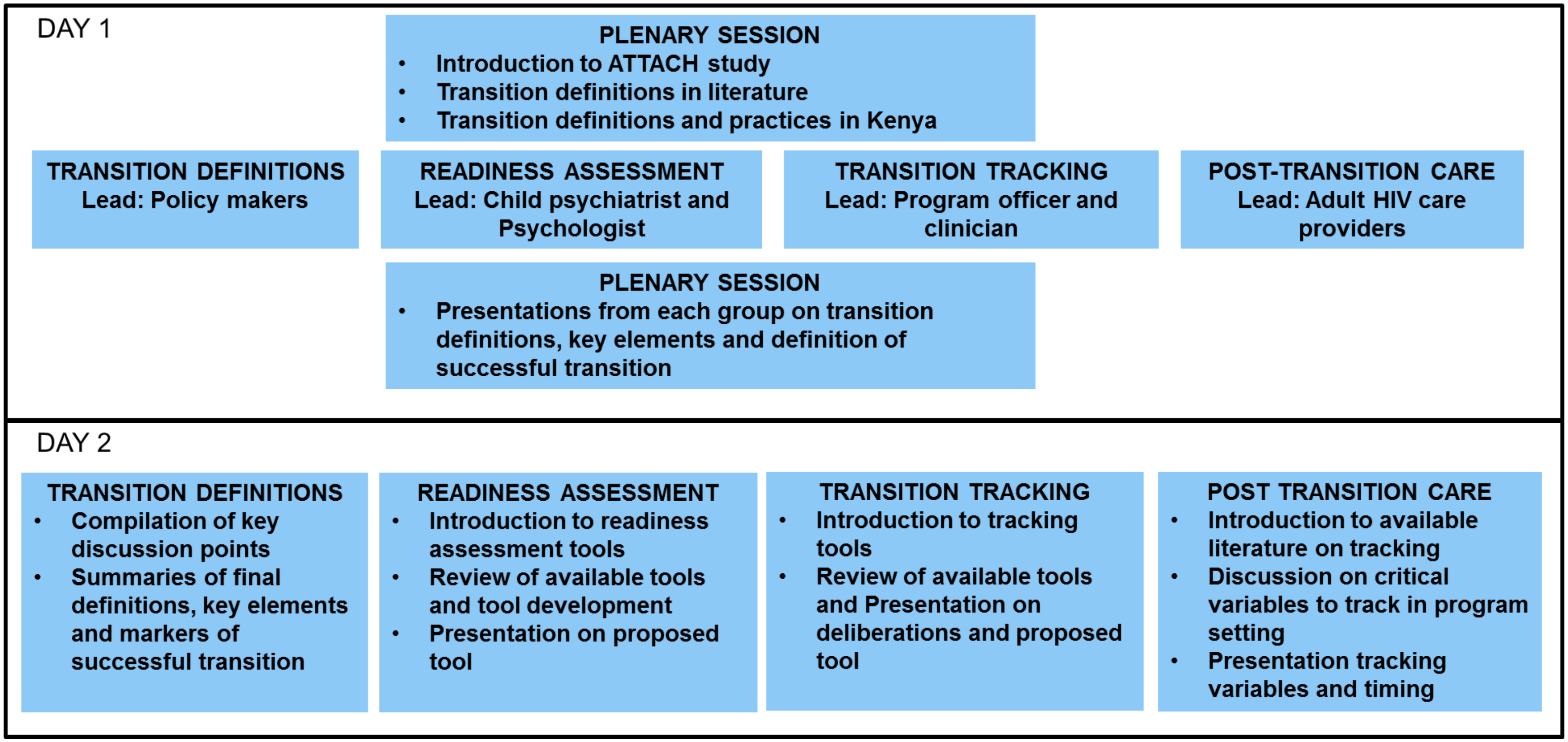


Table 1: Summary of transition elements and definitions of successful transition

Key elements of transition	
Start date	Soon after disclosure, preferably from age 14
Stop date	Target age 25 but consider developmental milestones
Readiness assessment	Assessed by health care worker from age 17 Key features of readiness • HIV literacy • Optimized ART regimen • Stable patient • Holistic approach • Willingness to transition
Caregiver readiness	Caregivers must be willing to allow adolescents to take responsibility for health
Communication with adult clinic	Awareness of adult clinic of the adolescents being transitioned to their clinic
Flexibility to return to adolescent services	At age 18-25, adolescents can receive services in adolescent clinics if they are uncomfortable in the adult clinics
Group transition	Group transition and support groups where possible
Special considerations	Process can be slower or faster for pregnant adolescents, those with delayed/early milestones adolescents with disability
Definition of successful transition	Include the following: • Linkage to care • Retention • Viral suppression

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