

Virological and Social Outcomes of HIV-Infected Adolescents and Young Adults in The Netherlands Before and After Transition to Adult Care

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Background. As a result of effective combination antiretroviral therapy (cART) and advanced supportive healthcare, a growing number of human immunodeficiency virus (HIV)-infected children survive into adulthood. The period of transition to adult care is often associated with impaired adherence to treatment and discontinuity of care. We aimed to evaluate virological and social outcomes of HIV-infected adolescents and young adults (AYAs) before and after transition, and explore which factors are associated with virological failure.

Methods. We included 59 HIV-infected AYAs from the Netherlands who had entered into pediatric care and transitioned from pediatric to adult healthcare. We used HIV RNA load and cART data from the Dutch Stichting HIV Monitoring database (1996–2014), and collected social and treatment data from patients' medical records from all Dutch pediatric HIV treatment centers and 14 Dutch adult treatment centers involved. We evaluated risk factors for virological failure (VF) in a logistic regression model adjusted for repeated measurements.

Results. HIV VF occurred frequently during the study period (14%–36%). During the transition period (from 18 to 19 years of age) there was a significant increase in VF compared with the reference group of children aged 12–13 years (odds ratio, 4.26 [95% confidence interval, 1.12–16.28]; $P = .03$). Characteristics significantly associated with VF were low educational attainment and lack of autonomy regarding medication adherence at transition.

Conclusions. HIV-infected AYAs are vulnerable to VF, especially during the transition period. Identification of HIV-infected adolescents at high risk for VF might help to improve treatment success in this group.

Keywords. HIV; adolescents; young adults; transition; virological outcomes.

As a result of potent combination antiretroviral therapy (cART) and advanced supportive healthcare, a growing number of human immunodeficiency virus (HIV)-infected children survive into adulthood. Therefore, the transitioning process of these chronically ill adolescents, often defined as “the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-orientated health care systems” [1], has become increasingly important.

Although there is no universal age range to comprise adolescence, it is often defined as the period that starts around 10 years of age and ends around the age of 19 years [2]. However, research

on adolescent neurocognitive development and behavior increasingly supports the extension of this age range from the age of 13 to 24 years [3, 4].

In the Netherlands, similar to a large number of countries worldwide, an adolescent formally reaches the adult age at 18 years, and will then transfer from pediatric to adult healthcare. The process of transition can be especially challenging in chronically ill adolescents, partly due to dependence on caregivers and healthcare services, developmental difficulties, and psychosocial delays [5]. Potential problems during and after transition are loss of a patient to follow-up, rebellion to treatment resulting in nonadherence, and discontinuity of care due to insufficient communication between healthcare workers (HCWs) [6]. Studies including HIV-infected adolescents and young adults (AYAs), family members, and HCWs reported similar problems after transition, including risk of nonadherence to medication, lack of autonomy, ignorance of new healthcare systems, and problems with handling of insurance due to changed conditions after legally reaching adulthood [7–10]. This is

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further illustrated by a recent study in perinatally HIV-infected youths in the United Kingdom, suggesting the transition period as a critical time for adherence support to maintain immune function [11]. Additionally, HIV-infected adolescents generally have complex medical needs and treatment histories different from those of newly HIV-infected adults [12]. Various factors may ease the transition process and improve patient outcomes, including early initiation of the transition process and utilization of a transition protocol [10, 13].

Healthcare for HIV-infected children in industrialized countries is usually organized in a multidisciplinary and family-centered way, with ample supportive care available [9, 14, 15]. In the Netherlands, HIV pediatric care is centralized in 4 pediatric HIV treatment centers. Transition protocols have been adjusted over the years in each center, but several services were uniformly offered during pediatric HIV care and transition to adult care. These include early focus on independence regarding management of disease, knowledge of disease, and the possibility to meet adult healthcare workers prior to formal transition. Treatment adherence support is offered in both pediatric and adult care during the quarterly outpatient clinic appointments, and additionally via telephone calls, emails, and text messages, dependent on personal needs. HIV-infected AYAs can participate in peer group meetings, with several nationwide activities organized each year.

In case of consistent nonadherence in children and AYAs <18 years, nonvoluntary measures can be taken, such as the use of directly observed therapy (DOT) and temporary outplacement of children in foster homes for monitoring of proper medication intake [14].

Studies evaluating the outcomes of HIV-infected AYAs after transition from pediatric to adult healthcare are scarce. One study showed increased adherence problems and a decreasing self-reported CD4⁺ T-cell count after transition [9]. Another small study on the outcomes of 17 HIV-infected AYAs reported consistent treatment adherence and virological control post-transition, whereas attendance rates declined [16].

This study aimed to evaluate long-term nationwide virological and social outcomes of HIV-infected AYAs before and after transition from pediatric to adult healthcare in the Netherlands, and to explore factors associated with virological outcomes.

METHODS

We included 59 HIV-infected patients from all 4 pediatric HIV treatment centers in the Netherlands (Academic Medical Center, Amsterdam; University Medical Center, Utrecht; Erasmus Medical Center, Rotterdam; and University Medical Center, Groningen). Patients were included if they had been in pediatric care, had received cART while in pediatric care, and had completed transition into adult healthcare. The moment of transition was defined as the first clinical visit in adult care. Patients linked to care gave informed consent to their current

healthcare provider. HIV-related and cART-related data were collected from the Stichting HIV Monitoring database (SHM), the Dutch national HIV registry. HIV specialist nurses from both pediatric and adult HIV treatment centers obtained additional demographic and social data from patient files using standardized questionnaires. This included level of knowledge of HIV at the moment of transition (ie, the difference between HIV infection and AIDS, the various HIV transmission routes, basic knowledge of the HIV-affected immune system, basic knowledge of cART and resistance, preventive measures to reduce transmission), classified as sufficient or insufficient as documented by HIV specialist nurses, and level of autonomy regarding medication adherence at the moment of transition (ie, being independent of caregivers or institutions and monitored by the HIV specialist nurse). These topics were routinely evaluated during patient visits. In addition, employment status and participation in a peer group for people living with HIV were documented. Information on use of adherence support and number of missed appointments per year was collected from patient files. HIV RNA load measurements were collected every 3 months during pediatric care, and every 3–6 months during adult care. Baseline data collection started from the age of 12 years, or from the first available pediatric healthcare visit if the study participant was >12 years but <18 years at entry into clinical care. Demographic and social data were collected at baseline, at transition, and at the end of study, defined as either 6 years after transition or at the study closure date on 1 November 2014, whichever came first. Socioeconomic status (SES) was classified as high, middle, low, and very low, according to area codes as described by the Netherlands Institute for Social Research [17]. Educational attainment was classified by using the International Standard Classification of Education (ISCED 2011) [18], in 4 categories: unknown, low (primary, lower secondary, and special education), middle (upper secondary), and high (postsecondary and short-cycle tertiary).

Statistical Analyses

HIV virological failure (VF) was defined as 2 consecutive HIV RNA measurements >400 copies/mL. We assessed VF for each year starting 6 months after cART initiation, with age ranging from 12 to 25 years. Years of being under clinical observation ranged from –8 to 6, with 0 being the year of transition. Years –8 to –1 were the years before the transfer year, and years 1–6 were the years after transfer to adult care. Age was included according to the age in a specific year prior to, during, or after transition to adult care. Patients were allowed to contribute to multiple years as they aged and were under clinical observation during several years.

Risk factors for VF were analyzed using a logistic regression model, using the generalized estimating equation (GEE) method with a logit link function and an exchangeable correlation structure to adjust for correlations between years of age of the

Table 1. Demographic Characteristics of Human Immunodeficiency Virus-Infected Adolescents (N = 59) Transitioning From Pediatric to Adult Healthcare in The Netherlands

Characteristic	No. (%)
Female sex	34 (58)
Age at HIV diagnosis, y, median (IQR)	8 (3–13) ^a
Age at cART initiation, y, median (IQR)	10 (7–14) ^b
Age at start of data collection, y, median (IQR)	12 (12–13)
Age at end of study, y, median (IQR)	22 (21–26)
Age at disclosure of diagnosis, y, median (IQR)	12 (11–14)
Transition age, y, median (IQR)	19 (18–20)
Follow-up time, y, median (IQR)	10 (8–12)
Lost to follow-up	8 (14)
Country or region of birth	
Netherlands	23 (39)
Sub-Saharan Africa	28 (48)
Asia	3 (5)
Latin America and Caribbean	2 (3)
Other ^c	3 (5)
Biological mother deceased ^d	
No	32 (54)
Yes	21 (36)
Unknown	6 (10)
Biological father deceased ^d	
No	31 (53)
Yes	15 (25)
Unknown	13 (22)
HIV transmission route	
Perinatal	46 (78)
Sexual	4 (7)
Blood transfusion	2 (3)
Unknown	7 (12)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range.

^a n = 58.

^b n = 57.

^c North Africa, Middle East, and Western Europe (excluding Netherlands).

^d Parent deceased during childhood.

same individual due to repeated measurements. Bivariate GEE analyses were used to determine factors associated with VF. All variables with a *P* value <.20 in the univariate analysis were included in the multivariable model.

The age group 12–13 years was set as the reference group; this was the youngest age group. The following variables were included as time-updated variables: age at clinical visit, education at transition and end of study, employment, cumulative time of cART use, and being in pediatric or adult care. Patients with missing data regarding educational attainment (n = 6) were included in the analyses as a separate category. Missing data regarding SES (n = 2), HIV knowledge (n = 1), and cART autonomy (n = 2) were not included in the analyses.

Trend in missed appointments per year over time was tested using the Cochran-Armitage test for trend. Differences in medical and social characteristics between patients who were lost to

Table 2. Social Characteristics of Human Immunodeficiency Virus-Infected Adolescents and Young Adults (N = 59) Transitioning From Pediatric to Adult Healthcare in The Netherlands

Characteristic	Variable	No. (%)		
		Baseline	Transition	End of Study
Family composition	Both biological parents ± siblings	12 (20)		
	One biological parent	17 (29)		
	Blended family	3 (5)		
	Adoptive parents	6 (10)		
	Foster parents	13 (22)		
	Unaccompanied refugee minor	6 (10)		
	Residential institution	2 (3)		
	With parents (biological/adoptive/foster)			16 (27)
	Single			12 (20)
	With partner			11 (19)
	With partner + children			6 (10)
Single + children			3 (5)	
Other ^a			7 (12)	
Unknown			4 (7)	
Socioeconomic status	High	7 (12)		
	Middle	17 (29)		
	Low	16 (27)		
	Very low	17 (29)		
	Unknown	2 (3)		
Education ISCED 2011	Primary			1 (2)
	Lower secondary		32 (54)	16 (27)
	Upper secondary		23 (39)	20 (34)
	Postsecondary		2 (3)	
	Short-cycle tertiary		2 (3)	14 (24)
	Special education			2 (3)
	Unknown			6 (10)
Employment	Paid job			22 (37)
	Student			23 (39)
	Unemployed			3 (5)
	Receiver incapability benefit			5 (9)
	Unknown			6 (10)
	Peer group	Yes		29 (49)
No		30 (51)	47 (80)	
HIV knowledge ^b	Yes		55 (93)	
	No		2 (3)	
	Unknown		2 (3)	
cART autonomy ^c	Yes		43 (73)	
	No		15 (25)	
	Unknown		1 (2)	

Abbreviations: cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; ISCED, International Standard Classification of Education 2011.

^a With family other than parents, with friends, or in sheltered housing.

^b HIV disease knowledge checklist was used at transition and knowledge was categorized as “yes” if sufficient according to the HIV specialist nurse.

^c Patient was able to manage cART adherence without help from parents or professional home healthcare institution.

follow-up and who were still in care were tested using χ^2 or the Fisher exact test. Statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, North Carolina).

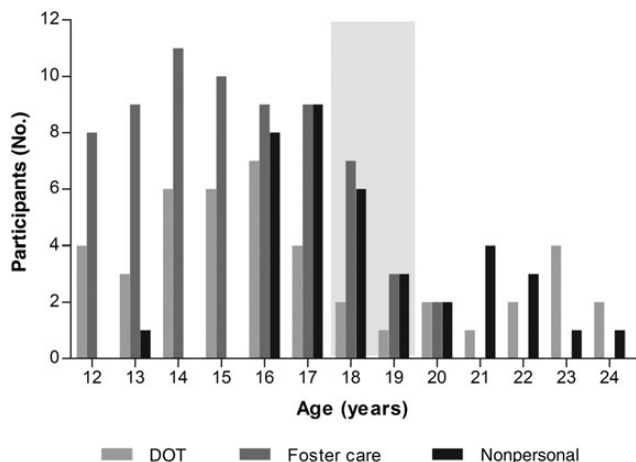


Figure 1. Different forms of adherence support utilized during the study period. Adherence support included additional support by foster care if parents or caretakers were unable to support medication intake; directly observed therapy (DOT) under supervision of a professional home healthcare institution; or nonpersonal adherence support, which included telephone reminders, text messages, and memory caps. The gray shaded area represents the age range in which transition to adult care takes place.

RESULTS

Sociodemographic Characteristics

A total of 72 HIV-infected AYAs who had transitioned to adult healthcare were identified, of whom 59 were included. Reasons for exclusion were no permission to use social data from medical records ($n = 8$), missing data due to unreturned questionnaires ($n = 3$), and mental/physical disability requiring permanent treatment support ($n = 2$). Demographic characteristics of study participants are displayed in Table 1. The majority of children were born in sub-Saharan Africa (48%) or in the Netherlands (39%). The median age at HIV diagnosis was 8.4 years (interquartile range [IQR], 2.6–12.8 years), and cART was started at a median age of 10.4 years (IQR, 6.8–13.9 years). At baseline, more than half of the children lived with 1 or both biological parents, and a substantial part with adoptive or foster parents (32%). During pediatric care, Child Protection Service (CPS) had been involved with 36% of the children (data not shown). Transition to adult healthcare occurred at a median age of 18.8 years (IQR, 18.1–19.5 years). Social characteristics of participants at baseline, transition, and end of study are displayed in Table 2. At transition, 55 (93%) of AYAs demonstrated sufficient knowledge of HIV disease, and 43 (73%) had sufficient autonomy regarding medication adherence. After transition, 8 (14%) patients were lost to follow-up after a mean follow-up time of 1.5 years (range, 0–5 years) after transition, and are currently not linked to care in the Netherlands.

Treatment and Supportive Care

Figure 1 shows different forms of adherence support as received by our study sample over time. Temporary placement in foster homes for the explicit reason of securing medication intake was

exclusively used before transition in a maximum of 11 patients (19%) at the age of 14 years. DOT was used in a maximum of 7 patients (12%) at the age of 16 years, but only in exceptional cases and on a voluntary basis after transition. From the age of 16 years, nonpersonal support was the most common type of support care. The mean amount of missed appointments per year per individual increased significantly from 0.2 at baseline to 1.3 at end of study ($P < .001$; [Supplementary Figure 1](#)).

Virological Failure in Relation to Demographic and Social Characteristics

Of 59 included patients, 58 were included in the GEE analysis assessing the association between demographic and social characteristics and VF. One patient started cART during pediatric care, but had transitioned to adult care within 6 months after starting cART, and therefore did not meet our criteria for VF assessment. Factors associated with VF are displayed in Table 3. VF occurred most frequently in adolescents aged 18–19 years and was concentrated around and shortly after transition (odds ratio [OR], 4.26 [95% confidence interval {CI}, 1.12–16.28], $P = .03$; Figure 2). AYAs with low educational attainment were more likely to experience VF compared with adolescents with middle or high educational attainment (OR, 3.32 [95% CI, 1.39–7.92], $P = .007$). Furthermore, AYAs with unknown educational attainment were significantly more likely to experience VF (OR, 6.23 [95% CI, 2.04–18.9]). Four of the 6 patients with unknown educational level were lost to follow-up. Patients lacking autonomy regarding medication adherence at transition experienced VF more than patients autonomous in medication intake (OR, 6.89 [95% CI, 2.57–18.5], $P < .001$). In addition, those with insufficient HIV knowledge were more likely to experience VF (OR, 5.15 [95% CI, 2.16–12.3], $P < .001$), although it must be noted that this group was small ($n = 2$). No associations were found between VF and employment, cumulative cART use, family composition, SES, or participation in a peer group. Of all participants included in the analyses, 29 (50%) experienced VF according to our definition in pediatric care, of whom 20 (34%) also experienced VF in adult care. Of those who did not experience VF in pediatric care, only 2 (3%) experienced VF in adult care. There were no patients in our study without alternative cART options.

Loss to Follow-up After Transition

In total, 8 AYAs (14%) were lost to follow-up after transition. CPS was more frequently involved during childhood in AYAs who were lost to follow-up compared with those who remained in care (75% vs 29%, $P = .02$). Autonomy over cART intake was lower in AYAs lost to follow-up (50% vs 67%, $P = .02$; [Supplementary Figure 2](#)).

DISCUSSION

In our study, AYAs transitioning from pediatric to adult care were shown to be vulnerable to VF, especially around and

Table 3. Medical and Social Characteristics Associated With Virological Failure Before and After Transition

Determinant	Univariate Analysis ^a		Multivariable Analysis ^b	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Age				
12–13 y	1			
14–15 y	1.99 (.98–4.06)	.06	2.14 (.82–5.58)	.12
16–17 y	1.65 (.62–4.35)	.31	1.53 (.42–5.70)	.51
18–19 y	3.29 (1.26–8.76)	.02	4.26 (1.12–16.28)	.03
20–21 y	2.23 (.80–6.17)	.12	2.66 (.76–9.12)	.12
22–24 y	1.07 (.16–1.20)	.89	1.17 (.31–4.43)	.16
Sex				
Male	1		1	
Female	1.77 (.79–3.94)	.16	1.60 (.63–4.43)	.32
Birth region				
Netherlands	1			
Sub-Saharan Africa	1.73 (.70–4.22)	.36		
Other ^c	1.75 (.52–5.88)	.23		
Education				
Unknown	5.15 (2.31–11.7)	<.001	6.23 (2.04–18.9)	.001
Low	2.97 (1.37–6.42)	.005	3.32 (1.39–7.92)	.007
Middle	1		1	
High	1.45 (.57–3.78)	.43	1.53 (.55–4.35)	.40
Employment				
NA, child	1.03 (.61–1.77)	.90		
Paid job/student	1			
Other ^d	1.58 (.56–4.48)	.38		
Unknown	1.62 (.61–4.26)	.34		
Cumulative cART use				
Per-year increase	0.99 (.91–1.97)	.75		
Family composition at entry				
Biological parents	1		1	
1 biological parent ^e	1.69 (.44–6.42)	.44	1.15 (.23–5.75)	.86
Adoptive/foster parent(s)	2.56 (.73–8.94)	.14	1.17 (.28–5.00)	.82
Other ^f	3.78 (.81–18.0)	.09	3.63 (.63–20.9)	.15
Autonomy of cART at transition				
Yes	1		1	
No	4.30 (1.97–9.39)	<.001	6.89 (2.57–18.5)	<.001
HIV care				
Pediatric	1		1	
Adult	1.08 (.68–1.72)	.73	1.17 (.66–2.08)	.58
HIV knowledge				
No	4.22 (2.63–7.14)	<.001	5.15 (2.16–12.3)	<.001
Yes	1		1	
SES				
High	0.48 (.04–5.20)	.55		
Middle	1			
Low	0.55 (.11–2.82)	.47		
Very low	0.34 (.56–2.10)	.25		
Peer group				
No	1			
Yes	1.36 (.69–2.74)	.37		

Abbreviations: cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; NA, not applicable; OR, odds ratio; SES, socioeconomic status (defined by area code).

^a n = 58: Patients with missing data regarding SES (n = 2), HIV knowledge (n = 1), and cART autonomy (n = 2) were not included in the specific univariate analyses assessing the association between SES, HIV knowledge, or cART autonomy and virological failure.

^b n = 56: Patients with missing data regarding HIV knowledge (n = 1) and cART autonomy (n = 2) were excluded from the multivariable analyses.

^c North Africa, Middle East, and Western Europe (excluding the Netherlands).

^d Unemployed or receiving an incapability benefit.

^e Living with 1 biological parent or in a blended family.

^f Unaccompanied minor refugee or living in a residential institution.

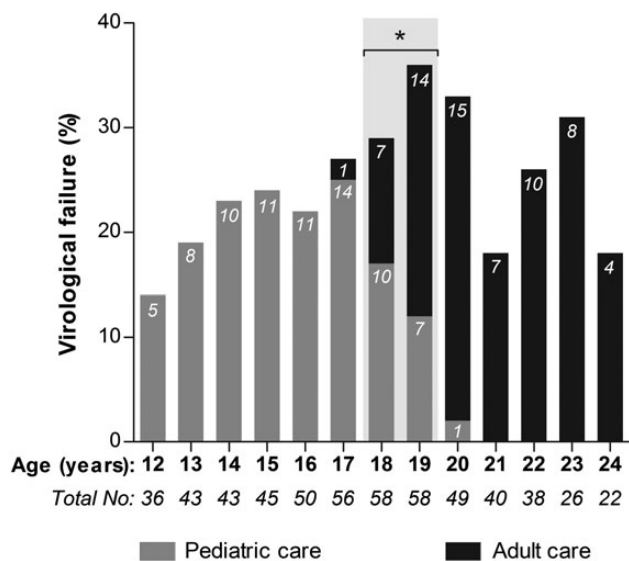


Figure 2. Rates of virological failure. The percentage of patients in pediatric care (gray) and adult care (black) experiencing virological failure, defined as 2 consecutive human immunodeficiency virus RNA measurements >400 copies/mL in 1 year. The number of patients per age group is displayed below the graph, and the amount of patients experiencing virological failure in each age group is represented by the numbers inside the bars. Age 18–19 years was identified as a risk factor for virological failure in a logistic regression model, using the generalized estimating equation method to adjust for correlations between years of age of the same individual. The gray shaded area represents the age range in which transition to adult care takes place for most patients. * $P < .05$.

shortly after the transition period. However, of 29 participants who had never experienced VF in pediatric care, only 2 participants experienced VF in adult care. In addition, of those 29 who did experience VF in pediatric care, 20 also experienced VF in adult care. These outcomes show that good adherence in pediatric care is a predictor for adherence after transition and that the effect of transition on VF is probably limited. A common result of VF is limitation of treatment possibilities with potentially severe consequences, such as disease progression and death. Indeed, a study on mortality in HIV-infected AYAs after transition showed that of 11 AYAs who died during the study period, 9 experienced VF due to poor treatment adherence when in pediatric care, despite available treatment possibilities [19]. Addressing transition-specific issues before transition does not seem to guarantee optimal virological suppression. At the age of 18 years, an individual is still developing independence and self-awareness, which increases the risk of suboptimal care [20]. Prolonged care at a pediatric treatment center may be an option to prevent VF in specific cases, but legislation in the Netherlands offers limited opportunities to do so.

Consistent with other cohorts of HIV-infected AYAs in industrialized countries, a large number of AYAs in our cohort originated from sub-Saharan Africa, had lost 1 or both biological parents, and were perinatally HIV infected [9, 12, 21].

Additionally, they were often adopted or in foster care during childhood [22]. We found several associations between social characteristics and virological outcomes. A higher educational level was associated with better virological outcomes. This finding supports the notion that school success is important for successful transition into adulthood [22]. Indeed, higher education and being employed were shown to have a positive influence on treatment adherence [23]. Previous studies report that intelligence scores and cognitive functioning of HIV-infected children are poorer compared with uninfected children [24–26]; moreover, a higher risk for cognitive impairment is reported for HIV-infected youths with a history of CDC class C disease [27]. These findings may negatively impact their educational achievement and increase their risk of VF.

Our study shows that VF is associated with low levels of autonomy regarding medication adherence and disease knowledge, although the number of participants with insufficient disease knowledge was low ($n = 2$), warranting verification of this association in a larger sample. Nonetheless, increased focus on disease knowledge, self-management, and adequate communication between patients and their pediatric and adult HCWs has been suggested to positively influence post-transitional outcomes [7, 8, 28]. Additionally, research focusing on successful transition emphasized the importance of behavioral indicators, such as keeping medical appointments and demonstrating ownership of medical care [29]. The number of missed appointments increased during our study period, and was higher during adult care compared with pediatric care. However, missing 2 or more appointments yearly did not lead to fewer clinical visits in that year than required for standard care, and therefore there was no higher chance of missing VF in that group.

In our study, the 8 patients who were lost to follow-up showed poorer social outcomes regarding involvement of CPS and autonomy toward cART adherence. Factors previously reported to be associated with loss to follow-up were being in adult care as compared to pediatric care, higher HIV RNA load, visiting the outpatient clinic <4 times per year, and not being prescribed cART [30]. These findings suggest that specific social characteristics make AYAs more vulnerable to loss to follow-up, which may further increase their risk of VF.

To our knowledge, we are the first to describe virological and social characteristics in a diverse HIV-infected AYA population over a follow-up period of up to 13 years. The strength of this study is the use of data from usually separated pediatric and adult healthcare systems. This was possible because of the historically robust national HIV registry (SHM) and close collaborations between different pediatric and adult HIV treatment centers in the Netherlands.

Nonetheless, this study has some limitations. The sample size is relatively small, and further research on factors associated with VF is therefore needed to affirm our outcomes. Although

the levels of knowledge of HIV disease and treatment autonomy were assessed by trained HIV specialist nurses, they are subjective qualifications [31]. However, we demonstrate that HIV-infected AYAs are at higher risk of VF around transition to adult care. Identification of at-risk HIV-infected AYAs with low educational level, low HIV knowledge, poor treatment autonomy, and VF in pediatric care may improve sustained treatment success in this vulnerable group. Last, long-term nonprogressors were not included in our study, as VF cannot be measured in this group.

Supporting adolescents in the process of becoming autonomous regarding medication adherence should begin during pediatric care and requires continuous attention. Monitoring of treatment adherence and appointment attendance is mandatory in AYAs both before and after transition. As education and employment are associated with better treatment adherence and success, addressing these topics during transition, and providing additional support where necessary and possible, may further improve virological outcomes in this population.

Supplementary Data

Supplementary materials are available at <http://cid.oxfordjournals.org>. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Author contributions. A. M. W. designed and performed the study, collected the data, and wrote the manuscript. C. S. performed the statistical analysis. S. C., F. W. N. M. W., and C. B. revised and edited the manuscript. M. M., L. C. K., L. M. Z., B. Z., N. N., J. C. P., M. H. J. K.-J., and E. P. S. provided and collected the largest share of virological, treatment, and social data and edited the manuscript. D. P. supervised and designed the study, provided the data, and revised and edited the manuscript. Members of the Dutch HIV AYA Study Group provided and collected virological, treatment, and social data and edited the manuscript.

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References

1. Blum RW, Garell D, Hodgman CH, et al. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. *J Adolesc Health* 1993; 14:570–6.
2. World Health Organization. WHO adolescent health. Available at: http://www.who.int/topics/adolescent_health/en/. Accessed 23 July 2016.
3. Arnone JM. Adolescents may be older than we think: today 25 is the new 18, or is it? *Int J Celiac Dis* 2014; 2:47–8.
4. Centers for Disease Control and Prevention. Sexually transmitted diseases: adolescents and young adults. Available at: <http://www.cdc.gov/std/life-stages-populations/adolescents-youngadults.htm>. Accessed 21 June 2015.
5. Rosen DS, Blum RW, Britto M, Sawyer SM, Siegel DM. Transition to adult health care for adolescents and young adults with chronic conditions. *J Adolesc Health* 2003; 33:309–11.
6. van Staa A. On your own feet. Available at: <http://www.oepenbenen.nu/nl/zorg/transitie-in-zorg/>. Accessed 23 July 2016.
7. Vijayan T, Benin A, Wagner K, Romano S, Andiman W. We never thought this would happen: transitioning care of adolescents with perinatally-acquired HIV infection from pediatrics to internal medicine. *AIDS Care* 2009; 21:1222–9.
8. Gilliam PP, Ellen JM, Leonard L, Kinsman S, Jevitt CM, Straub DM. Transition of adolescents with HIV to adult care: characteristics and current practices of the Adolescent Trials Network for HIV/AIDS interventions. *J Assoc Nurses AIDS Care* 2011; 22:283–94.
9. Wiener LS, Kohrt B-A, Battles HB, Pao M. The HIV experience: youth identified barriers for transitioning from pediatric to adult care. *J Pediatr Psychol* 2011; 36:141–54.
10. Maturio D, Powell A, Major-Wilson H, Sanchez K, De Santis JP, Friedman LB. Development of a protocol for transitioning adolescents with HIV infection to adult care. *J Pediatr Health Care* 2011; 25:16–23.
11. Rebecca H, Ali J, Caroline F, et al. Clinical outcomes in adults with perinatal HIV after transfer from pediatric care. In: Conference on Retroviruses and Opportunistic Infections, Boston, MA, 22–25 February 2016. Abstract 835.
12. Foster C, Judd A, Tookey P, et al. Young people in the United Kingdom and Ireland with perinatally acquired HIV: the pediatric legacy for adult services. *AIDS Patient Care STDS* 2009; 23:159–66.
13. Office of the Medical Director, New York State Department of Health AIDS Initiative in Collaboration with the Johns Hopkins University Division of Infectious Diseases. Transitioning HIV-infected adolescents into adult care. 2012. Available at: <http://www.hivguidelines.org/clinical-guidelines/adolescents/transitioning-hiv-infected-adolescents-into-adult-care/>. Accessed 23 July 2016.
14. van der Plas A, Scherpier H, Kuijpers T, Pajkrt D. The effect of different intervention programs on treatment adherence of HIV-infected children, a retrospective study. *AIDS Care* 2013; 25:738–43.
15. Fair CD, Sullivan K, Dizney R, Stackpole A. 'It's like losing a part of my family': transition expectations of adolescents living with perinatally acquired HIV and their guardians. *AIDS Patient Care STDS* 2012; 26:423–9.
16. Eisen S, Barkley L, Schepers C, et al. Impact of transition to adult services on clinic attendance and virological control in HIV-infected adolescents. In: 15th Annual Conference of the British HIV Association. *HIV Med* 2009; 10:45.
17. The Netherlands Institute for Social Research. Neighbourhood status development in the Netherlands, 1998–2010. 2012. Available at: http://www.scp.nl/english/Publications/Summaries_by_year/Summaries_2012/Neighbourhood_status_development_in_the_Netherlands_1998_2010. Accessed 15 December 2015.
18. United Nations Educational, Scientific and Cultural Organization. The international standard classification of education 2011. Paris: UNESCO, 2013.
19. Fish R, Judd A, Jungmann E, O'Leary C, Foster C. Mortality in perinatally HIV-infected young people in England following transition to adult care: an HIV Young Persons Network (HYPNet) audit. *HIV Med* 2014; 15: 239–44.
20. Kapogiannis B, Xu J, Mayer KH, et al. The HIV continuum of care for adolescents and young adults (12–24 years) attending 13 urban US centers. Available at: http://www.natap.org/2015/IAS/IAS_42.htm. Accessed 13 October 2015.
21. Foster C, Waelbrouck A, Peltier A. Adolescents and HIV infection. *Curr Opin HIV AIDS* 2007; 2:431–6.
22. Andiman WA. Transition from pediatric to adult healthcare services for young adults with chronic illnesses: the special case of human immunodeficiency virus infection. *J Pediatr* 2011; 159:714–9.
23. Mathes T, Jaschinski T, Pieper D. Adherence influencing factors—a systematic review of systematic reviews. *Arch Public Health* 2014; 72:37.

24. Laughton B, Cornell M, Boivin M, Van Rie A. Neurodevelopment in perinatally HIV-infected children: a concern for adolescence. *J Int AIDS Soc* **2013**; 16:1–9.
25. Malee K, Williams PL, Montepiedra G, et al. The role of cognitive functioning in medication adherence of children and adolescents with HIV infection. *J Pediatr Psychol* **2009**; 34:164–75.
26. Cohen S, Ter Stege JA, Geurtsen GJ, et al. Poorer cognitive performance in perinatally HIV-infected children versus healthy socioeconomically matched controls. *Clin Infect Dis* **2014**; 60:1111–9.
27. Smith R, Chernoff M, Williams PL, et al. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. *Pediatr Infect Dis J* **2012**; 31:592–8.
28. Fair CD, Sullivan K, Gatto A. Best practices in transitioning youth with HIV: perspectives of pediatric and adult infectious disease care providers. *Psychol Health Med* **2010**; 15:515–27.
29. Fair CD, Sullivan K, Gatto A. Indicators of transition success for youth living with HIV: perspectives of pediatric and adult infectious disease care providers. *AIDS Care* **2011**; 23:965–70.
30. Agwu AL, Lee L, Fleishman JA, et al. Aging and loss to follow-up among youth living with human immunodeficiency virus in the HIV research network. *J Adolesc Health* **2015**; 56:345–51.
31. Bangsberg DR, Hecht FM, Clague H, et al. Provider assessment of adherence to HIV antiretroviral therapy. *J Acquir Immune Defic Syndr* **2001**; 26:435–42.