



Adolescent HIV treatment in South Africa's national HIV programme: a retrospective cohort study

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Summary

Background The number of South African adolescents receiving HIV care and treatment in South Africa is growing. By use of routinely collected laboratory data from South Africa's National HIV Programme, we aimed to quantify the numbers of adolescents accessing HIV care and treatment over time, characterise the role of perinatal infection in these trends, and estimate proportions of adolescents seeking HIV care and antiretroviral therapy (ART) in South Africa's public sector.

Methods We did a retrospective, descriptive cohort study of children and adolescents aged 1–19 years accessing care in South Africa's public sector HIV treatment programme from 2005 to 2016 with a CD4 cell count or viral load recorded in South Africa's National Health Laboratory Service database. We estimated the total number of children and adolescents entering HIV care with a CD4 cell count or viral load test result by calendar period, as well as the proportion in care and receiving ART with at least one viral load test result. We stratified analyses by gender and by whether the patient entered care at younger than 15 years (probably perinatally infected) or at 15–19 years (probably infected in adolescence).

Findings We identified 730 882 patients aged 1–19 years at entry to care between Jan 1, 2005, and Dec 31, 2016. 209 205 (54%) of 388 439 patients entering care younger than 15 years and 301 242 (88%) of 342 443 patients entering care aged 15–19 were female. During the study period, the number of virologically monitored patients aged 15–19 years receiving ART increased from 7949 in 2005–08 to 80 918 in 2013–16. 92 783 (66%) of 140 028 patients aged 15–19 years seeking care started ART by 2016, well below UNAID's target of ART for 90% of those diagnosed. We project that the number of adolescents on ART will continue to rise.

Interpretation The many adolescents aged 15–19 years receiving ART reflect the ageing of children entering care at ages 1–14 years, and increases in care-seeking among horizontally infected adolescents aged 15–19 years. However, many adolescents seeking care do not start ART, suggesting an urgent need for interventions to increase uptake of ART and improve services for this population.

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Introduction

Epidemic control in South Africa will require considerable expansion of treatment for adolescents to break HIV transmission cycles and reach the promise of an AIDS-free generation.¹ In 2016, around 10·2 million adolescents aged 10–19 years lived in South Africa.² Despite widespread access to HIV treatment and prevention services, South African youths aged 15–24 years face marked challenges in achieving the national targets of 90% tested, 90% on antiretroviral therapy (ART), and 90% virally suppressed by 2020. Adolescent girls have the highest HIV prevalence of any demographic group.³ The HIV disease burden previously noted in vertically infected children is predicted to shift to adolescent age groups as widespread access to paediatric ART reduces mortality, and slow progressors survive untreated.^{4,5} A global meta-analysis⁶ estimated median age at ART initiation of 7·9 years in perinatally infected children. Evidence suggests^{7,8} that adolescents in southern Africa are a susceptible group with unique

challenges in accessing testing, timely initiation of ART, successful adherence to treatment, and retention in HIV care programmes.^{7–12}

The ability to monitor trends in adolescent care-seeking has been limited by the absence of national longitudinal data. In partnership with South Africa's National Health Laboratory Service (NHLS), we created a National HIV Cohort through novel record linkage of the complete laboratory records of the national HIV programme.¹³ This longitudinal database includes all CD4 cell counts and HIV viral loads of all children and adolescents accessing public sector HIV care and treatment. By analysing these data, we aimed to quantify increases in children and adolescents accessing HIV care and treatment, characterise trends in the age distribution of this population over time with respect to patients who entered HIV care aged 1–14 years (probably perinatal transmission) and patients who entered HIV care aged 15–19 years (probably adolescent sexual transmission);

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Research in context

Evidence before this study

We did two searches on the PubMed database for articles published between Jan 1, 2004, and April 30, 2019, using the search terms "HIV", "adolescents", "treatment outcomes", and "South Africa"; and "HIV", "adolescents", "transmission", "South Africa". These papers indicated growing awareness of the importance of adolescent populations with HIV in South Africa and their key role in national epidemic control, particularly among girls. The 2017 Human Sciences Research Council South African National HIV Prevalence, Incidence, Behaviour and Communication survey estimated that 5.8% of the 2.5 million women and girls aged 15–19 years in South Africa had HIV, increasing to 15.6% in women aged 20–24 years. However, less is known about adolescent care-seeking patterns, as few large-scale cohorts are available. Data from an HIV cohort developed from South Africa's National Health Laboratory Service database was used in 2018 to describe care-seeking and retention in HIV care programmes among adults infected with HIV who access care in South Africa's national treatment programme.

Added value of this study

We describe and quantify the adolescent population accessing care in South Africa, using the complete laboratory records from South Africa's public sector treatment programme. Our results show a ten times increase in adolescents aged 15–19 years receiving HIV treatment between 2005 and 2016. This increase is due to the survival of perinatally infected children receiving antiretroviral therapy (ART) and an increase in care-seeking among adolescent girls and young women. We identified low progression to treatment initiation in patients aged 15–19 years.

Implications of all the available evidence

Increased HIV care-seeking among adolescents is encouraging, provided the health system is sufficiently prepared to meet the needs of this population. However, low rates of successful ART initiation in patients aged 15–19 years entering care suggest an urgent need to improve services for adolescents.

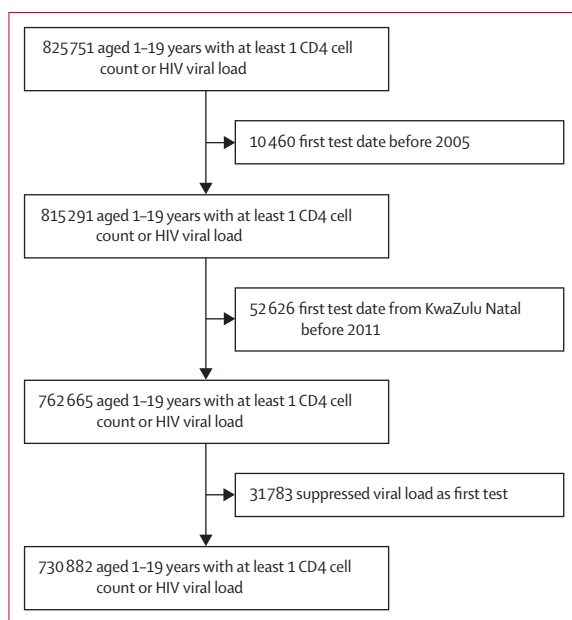


Figure 1: Flow chart of patients included in analysis

and estimate proportions of these patients in care who are receiving ART. Finally, we project probable numbers of adolescents on ART until 2021 based on these trends.

Methods

Study design

In this retrospective cohort study, we obtained data from the NHLS, which does all laboratory monitoring for South Africa's national public sector HIV programme. The NHLS Corporate Data Warehouse (CDW) database

includes all CD4 cell counts and viral loads dating back before large-scale roll-out of HIV treatment in 2004 (except KwaZulu-Natal province, which contributed data from 2010 onwards). Data are captured from each individual laboratory requisition form at the time a blood sample is taken and include demographic information such as name, surname, gender, and date of birth. As the CDW database does not have unique patient identifiers, we developed and validated a linkage algorithm to identify unique patients (and their associated laboratory results) through the demographic data available^{14,15} using traditional deterministic and probabilistic as well as network-based linkage methodology.^{16,17} The algorithm was developed and validated for application to the approximately 54 million CD4 cell counts and viral load tests in the NHLS in 2004–16 and attained sensitivity of 94%, specificity of almost 100%, and positive predictive values of 99% relative to manually matched data. This linkage enables analysis of the NHLS database as a National HIV Cohort, with longitudinal follow-up of all laboratory-monitored patients (including adolescents) accessing care in South Africa's public sector HIV programme.

Participants

We identified children and adolescents aged 1–19 years who entered HIV care in South Africa's public sector with a recorded CD4 cell count or viral load between Jan 1, 2005, and Dec 31, 2016 (and from Jan 1, 2011, in KwaZulu-Natal province). Laboratory records for children younger than 1 year were excluded, as infants are often identified in the NHLS database using information about the mother, reducing linkage accuracy. We excluded patients whose first CD4 or viral load date was before the study period (ie, 2005, or before 2011 for KwaZulu-Natal

province, which contributed data from 2010 onward). Patients whose first recorded test was a suppressed viral load were also excluded, as they most probably started ART in the private sector before transferring into the national programme or had a previous CD4 cell count that was not correctly matched to them.

This cohort study involved secondary analysis of de-identified data collected as part of routine care. Analysis was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M150429) and Boston University Medical Campus Institutional Research Board (H-31968).

Variable definitions

Key steps of the care cascade can be imputed from laboratory data based on national treatment guidelines. During the study period, CD4 cell counts were assessed at clinical presentation to determine eligibility for ART initiation. Viral load monitoring was indicated for all patients on ART with the first viral load test at initiation (before 2008) or at 6 months after initiation (2008 and later).¹⁸ During the study period, patients in care but not yet receiving ART should have had at least one CD4 cell count per year, and patients on ART should have had at least one viral load test per year.

We defined entry into HIV care as the date of the first CD4 cell count or viral load test result in the NHLS database because this date would signify, at a minimum, that the participant accessed HIV testing and blood tests to determine eligibility for ART initiation. We defined patients as currently in HIV care if they had at least one CD4 cell count or viral load test result in the NHLS database in a given year, and defined participants as currently accessing ART if any viral load test had been recorded in the database in a given year. We additionally distinguished between whether a person newly initiated ART in a given year or whether they were continuing ART, having been on ART the previous year.

We defined probable mode of transmission on the basis of age at entry into HIV care, with patients entering care at age 1–14 years most likely vertically infected via perinatal mother-to-child transmission, and patients who entered care at age 15–19 years most likely horizontally infected via sexual transmission. To evaluate the accuracy of using age of entry to define these categories, we computed the gender ratio among patients entering care by age. Girls of all ages appear at greater risk of HIV infection than boys, with girls at birth more at risk of vertical infection^{19,20} and adolescent girls more likely to become newly infected with HIV.^{21,22}

Statistical analysis

We summarised patient characteristics using simple proportions and medians with IQRs, stratified by probable mode of infection. We then assessed changes in the composition of the population in care and receiving ART over time. We computed numbers of patients newly

	Age 1–4 years (n=166 211)	Age 5–9 years (n=125 012)	Age 10–14 years (n=97 216)	Age 15–19 years (n=342 443)
Gender				
Female	86 256 (52%)	66 739 (53%)	56 210 (58%)	301 242 (88%)
Male	79 955 (48%)	58 273 (47%)	41 006 (42%)	41 201 (12%)
CD4 cell count at entry to care (cells per μL)				
Median (IQR)	791 (434–1319)	478 (255–785)	354 (168–598)	409 (265–585)
0–100	7640 (5%)	13 179 (11%)	15 826 (16%)	22 395 (7%)
101–200	8363 (5%)	10 934 (9%)	12 358 (13%)	31 629 (9%)
201–350	16 006 (10%)	20 411 (16%)	19 656 (20%)	81 818 (24%)
>350	134 202 (81%)	80 488 (64%)	49 376 (51%)	206 601 (60%)

Data are n (%) unless otherwise specified. Infections in patients in all age groups from 1 to 14 years were probably by vertical transmission. Infections in patients aged 15–19 years were probably by horizontal transmission.

Table 1: Characteristics of 730 882 adolescents by age at entry to HIV care in South Africa from 2005 to 2016

	Age 1–4 years (n=166 211)	Age 5–9 years (n=125 012)	Age 10–14 years (n=97 216)	Age 15–19 years (n=342 443)
2005	8618 (34%)	6254 (24%)	2384 (9%)	8278 (32%)
2006	12 213 (33%)	8036 (22%)	3569 (10%)	13 164 (36%)
2007	14 321 (33%)	8767 (20%)	4337 (10%)	16 459 (38%)
2008	15 741 (29%)	9743 (18%)	5770 (11%)	22 305 (42%)
2009	15 642 (28%)	9751 (17%)	6262 (11%)	24 429 (44%)
2010	15 771 (25%)	10 531 (17%)	7622 (12%)	28 803 (46%)
2011*	19 842 (20%)	18 574 (19%)	15 095 (15%)	44 793 (46%)
2012	15 710 (19%)	13 871 (17%)	12 232 (15%)	40 408 (49%)
2013	13 367 (19%)	11 774 (16%)	10 431 (14%)	36 525 (51%)
2014	12 521 (18%)	10 390 (15%)	10 085 (15%)	35 942 (52%)
2015	11 864 (17%)	9409 (14%)	10 204 (15%)	37 325 (54%)
2016	10 601 (17%)	7912 (13%)	9225 (15%)	34 012 (55%)

Data are n (%). Infections in patients in all age groups from 1 to 14 years were probably by vertical transmission. Infections in patients aged 15–19 years were probably by horizontal transmission. Data include all children and adolescents with at least one CD4 cell count or viral load test. *Data from KwaZulu-Natal included only from 2011 onward.

Table 2: Adolescents aged 1–19 years entering HIV care in South Africa, stratified by calendar year of entry to care

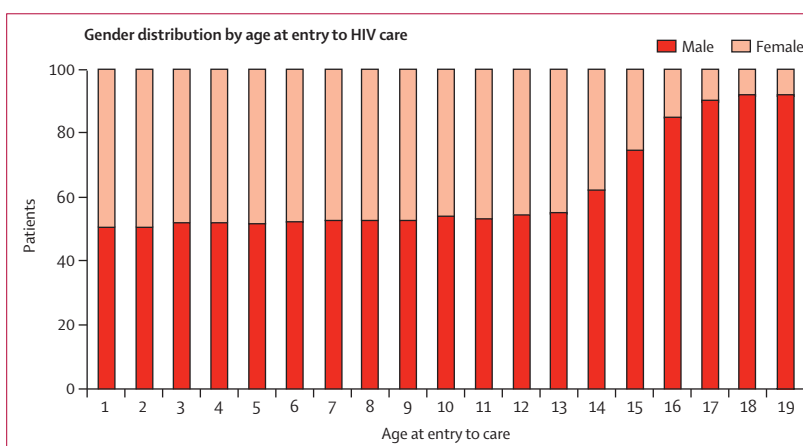


Figure 2: Gender distribution by age in years at entry to HIV care programme

initiating and continuing ART each year from 2005 to 2016, stratifying by probable mode of infection. We also assessed the age distribution of children and adolescents receiving ART in 2008, 2012, and 2016, chosen to represent an early, middle, and late cross-section in the scale-up of treatment in South Africa. Finally, we projected numbers of adolescents aged 15–19 years receiving ART into 2021 on the basis of past trends, in three scenarios: assuming no improvement in ART uptake or retention; assuming improvement in retention only; and assuming improvement in both ART uptake and retention (appendix p 1).

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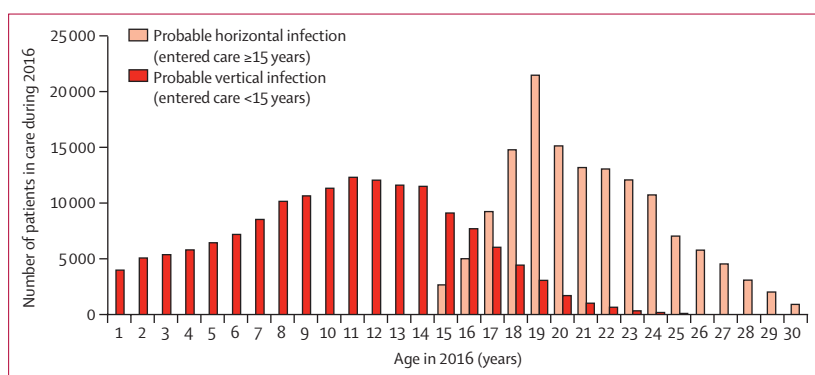


Figure 3: National distribution of age among children and adolescents in HIV care in 2016 in South Africa's public sector HIV programme, stratified by probable mode of infection

Patients younger than 15 years at entry to care were classified as having probable vertical (perinatal) transmission; patients aged 15 years or older at entry to care were classified as having probable incident horizontal infection.

The figure shows the current age distribution of all patients in care in 2016 who entered care aged 1–19 years at any point during 2005–16.

Analyses were done using SAS statistical software (version 9.4) and Microsoft Excel (version 16.16.5).

Role of the funding source

The funders had no role in study design, data collection, and data analysis and did not have any role in data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

After exclusions (figure 1), the NHLS National HIV Cohort included 730 882 patients aged 1–19 years who entered South Africa's public sector HIV programme with a first CD4 cell count or HIV viral load test result between Jan 1, 2005, and Dec 31, 2016 (table 1). These patients had 2·6 million CD4 cell counts and 2·2 million viral load results during the study period. Adolescents aged 15–19 years made up 47% (n=342 443) of the study population.

Patients entering into care increased steadily each calendar year until 2010, when they began to decline (table 2). The proportion of adolescents aged 15–19 years in the study population increased from 8278 (32%) of 25 534 in 2005 to 34 012 (55%) of 61 750 in 2016, reflecting increases in adolescent care-seeking and large declines in new patients entering care at younger ages, coinciding with the successful scale-up of prevention of mother-to-child transmission (PMTCT).

	Age 1–4 years	Age 5–9 years	Age 10–14 years	Age 15–19 years
2005–16 (all available data)				
Total patients (n)	166 211	125 012	97 216	342 443
Patients initiating ART	114 187/166 211 (69%)	87 632/125 012 (70%)	62 526/97 216 (64%)	151 537/342 443 (44%)
Male ART initiators out of all male patients	55 555/79 955 (69%)	41 943/58 273 (72%)	27 849/41 006 (68%)	17 265/41 201 (42%)
Female ART initiators out of all female patients	58 632/86 256 (68%)	45 689/66 739 (68%)	34 677/56 210 (62%)	134 272/301 242 (45%)
Total ART initiators 2005–08 out of all patients	25 803/50 893 (51%)	17 171/32 800 (52%)	7130/16 060 (44%)	7949/60 206 (13%)
Total ART initiators 2009–12 out of all patients	43 415/66 965 (65%)	33 475/52 727 (63%)	21 912/42 211 (52%)	28 688/138 433 (21%)
Total ART initiators 2013–16 out of all patients	44 969/48 353 (93%)	36 986/39 485 (94%)	33 484/39 945 (84%)	114 900/143 804 (79%)
2005–16 (excluding KwaZulu-Natal data)				
Total patients (n)	141 105	99 196	72 580	264 399
Total ART initiators 2005–16 out of all patients	94 483/141 105 (67%)	68 373/99 196 (69%)	45 028/72 580 (62%)	112 385/264 399 (43%)
Total ART initiators 2005–08 out of all patients	25 803/50 893 (51%)	17 171/32 800 (52%)	7130/16 060 (44%)	7949/60 206 (13%)
Total ART initiators 2009–12 out of all patients	36 224/55 496 (65%)	25 308/39 147 (65%)	15 291/29 521 (52%)	23 518/108 525 (21%)
Total ART initiators 2013–16 out of all patients	32 456/34 716 (93%)	25 894/27 249 (95%)	22 607/26 999 (84%)	80 918/95 668 (72%)
Data are n/N (%) unless otherwise specified. Infections in patients in all age groups from 1 to 14 years were probably by vertical transmission. Infections in patients aged 15–19 years were probably by horizontal transmission. ART=antiretroviral therapy. *ART initiator defined as having at least one viral load test observed during the period of entry to care as specified.				
Table 3: Patients aged 1–19 years starting ART* in South Africa, 2005–16, stratified by calendar period and age at entry to care				

Gender composition differed by age at entry into care, probably reflecting different modes of infection (figure 2). 152 995 (53%) of 291 223 patients entering care before age 10 years, 56 210 (58%) of 97 216 of those entering care at 11–14 years, and 301 242 (88%) of 342 443 of those entering care at 15–19 years were female. These patterns support our choice of age 15 years at entry into care as a cutoff for probable vertical versus probable horizontal infection.

We stratified the age distribution of patients in care in 2016 in South Africa's public sector HIV programme by probable mode of infection (figure 3). The peak of the age distribution at 10–14 years in children seeking care before age 15 years is consistent with a large cohort of children vertically infected in 2002–06, at which time PMTCT had not fully scaled up but when survival was increasing due to the rollout of paediatric ART. In 2016, this vertically infected population was just entering adolescence.

415 882 (57%) of 730 882 patients ages 1–19 years who entered HIV care in 2005–16 initiated ART as indicated by a record of at least one viral load test in the NHLS database (table 3). 55 555 (69%) of 79 955 boys and 58 632 (68%) of 86 256 girls entering care at ages 1–4 years initiated ART, compared with 41 943 (72%) of 58 273 boys and 45 689 (68%) of 66 739 girls entering care at ages 5–9 years, and 27 849 (68%) of 41 006 boys and 34 677 (62%) of 56 210 girls entering care at ages 10–14 years. Of patients entering care as older adolescents (15–19 years), the proportion of those initiating ART dropped for both girls (134 272 [45%] of 301 242) and boys (17 265 [42%] of 41 201).

The age distribution of children and adolescents receiving ART changed over the study period in two important ways (figure 4). First, the absolute number of children and adolescents on ART increased substantially from 2008 to 2016, with expansion of the national treatment programme. Second, there was a shift in the age distribution as vertically infected patients aged and as horizontally infected patients seeking care and starting ART increased.

These two trends led to large increases in adolescents aged 15–19 years receiving ART (table 3). Excluding KwaZulu-Natal data to ensure comparability, patients aged 1–4 years receiving ART increased from 25 803 in 2005–08 to 32 456 in 2013–16. Over the same period, patients aged 15–19 years receiving ART grew from 7949 patients in 2005–08 to 80 918 in 2013–16, a 10 times increase in adolescents receiving ART. Patients younger than 15 years starting ART rose steadily from 6262 to 16 875 new initiates in 2010, and then declined (table 4). New ART initiates among patients entering care at ages 15–19 years (presumably horizontally infected) increased from 519 in 2005 to 3784 in 2010, then continued to rise to 36 966 in 2016. By 2016, adolescents aged 15–19 years (presumably horizontally infected) accounted for nearly 60% (36 966 of 62 665) of all new ART initiators aged 1–19 years (table 4).

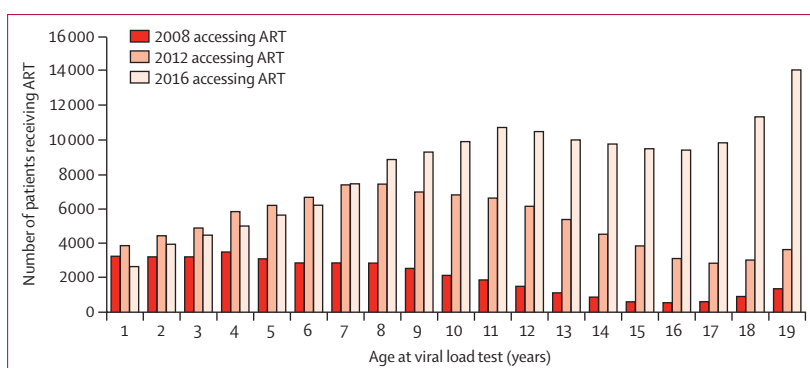


Figure 4: National distribution of age among children and adolescents receiving ART in South Africa's public sector HIV programme, stratified by calendar year
ART=antiretroviral therapy.

We estimated projected numbers of adolescents aged 15–19 years receiving ART in the public sector until 2021, based on the further ageing of vertically infected children into the 15–19-year age group and assumptions about care seeking, ART initiation, and retention in other age groups (figure 5). Based on existing trends, the number of adolescents on ART is expected to increase substantially. If both uptake of ART and retention on ART increased to their respective 90% targets, the number of adolescents on ART aged 15–19 years could nearly double in the 5 years between 2016 and 2021.

Discussion

Our results suggest three key findings. First, the number of adolescents aged 15–19 years receiving ART in South Africa increased by a factor of 10 between 2005–08 and 2013–16, and we expect it will continue to grow. Second, this peak in adolescent treatment is due to the confluence of two factors: the ageing of perinatally infected infants who entered HIV care in childhood and increasing numbers of adolescents aged 15–19 years seeking care for the first time (who were probably infected through sexual transmission). Third, our analysis found lower ART initiation among adolescents aged 15–19 years seeking care than in younger individuals, suggesting substantial scope to improve HIV care and treatment services for adolescents.

The success of previous HIV programmes is reflected in the peak of adolescents accessing HIV care in South Africa. The increase in adolescents receiving ART supports the idea that changes in eligibility criteria to include less-severely immunocompromised children and adolescents living with HIV have resulted in the expansion of the HIV treatment programme over time. The success of paediatric screening²³ and subsequent ART initiation among perinatally infected children has greatly increased survival of HIV-infected children. Supporting a meta-analysis,⁶ we found that many children enter care only in late childhood, having survived for many years without ART. Still, few would be expected to

	Probable vertical infection: age at entry to care 1–14 years					Probable horizontal infection: age at entry to care ≥15 years		
	Patients receiving ART out of all patients currently in care*	Age at test: 1–14 years		Age at test: 15–19 years†		Age at test: 15–19 years		
		Patients newly initiating ART‡	Patients continuing ART§	Patients newly initiating ART‡	Patients continuing ART§	Patients receiving ART out of all patients currently in care*	Patients newly initiating ART‡	Patients continuing ART§
2005	6262/17 256 (36%)	6262	0	0	0	519/8278 (6%)	519	0
2006	16 144/32 228 (50%)	12 227	3869	23	25	1761/15 288 (12%)	1562	199
2007	25 270/45 780 (55%)	14 432	10 604	60	174	3033/21 753 (14%)	2291	742
2008	35 655/60 280 (59%)	16 986	18 027	114	528	8180/32 126 (25%)	3577	1570
2009	42 111/71 756 (59%)	14 782	25 965	131	1233	6210/39 519 (16%)	3525	2685
2010	50 057/84 680 (59%)	16 875	30 894	209	2079	7213/52 269 (14%)	3784	3429
2011¶	74 419/115 745 (64%)	33 376	36 991	495	3557	13 310/78 177 (17%)	8422	4888
2012	90 106/124 688 (72%)	32 057	51 169	877	6003	21 722/87 840 (25%)	12 957	8765
2013	103 520/132 544 (78%)	30 446	62 144	1211	9719	53 337/96 377 (55%)	16 919	14 696
2014	115 060/140 126 (82%)	28 672	70 124	1438	14 826	45 942/109 222 (42%)	23 263	22 679
2015	126 625/150 048 (84%)	26 052	76 863	1921	21 789	73 317/126 540 (58%)	37 752	35 565
2016	135 058/155 229 (87%)	23 612	80 794	2087	28 565	92 783/140 028 (66%)	36 966	55 817

Data are n/N (%) or n. ART=antiretroviral therapy. *The population of patients currently in care was defined as number of patients with at least one CD4 cell count or viral load observed during the specified calendar year. †Patients who were aged 1–14 years at first entry to care but entered the older age group during the observation period. ‡A patient was defined as a new ART initiator if they had a first viral load test observed in database during that calendar year. §Continuing on ART was defined as any viral load test subsequent to the first viral load test observed during year after the initiating year. ¶Data from KwaZulu Natal included only from 2011 onward.

Table 4: Prevalent number of patients on ART stratified by calendar year, mode of infection, and age category

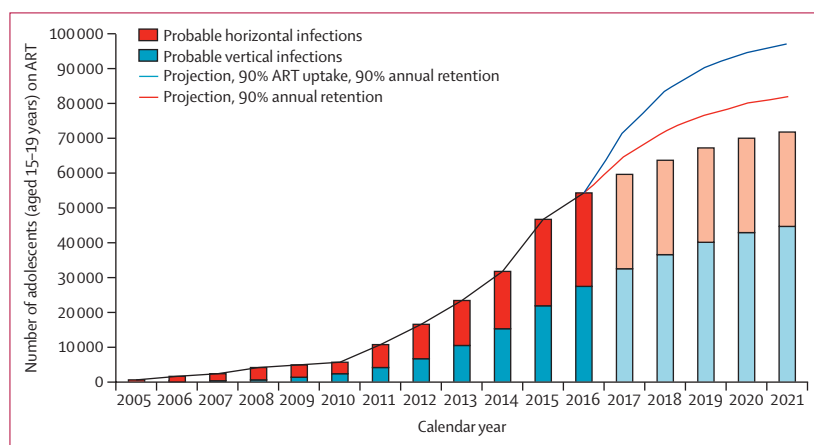


Figure 5: Projected adolescents aged 15–19 years receiving ART in South Africa

Solid black line above the columns for 2005–16 reflects observed trends in numbers of patients receiving ART. All data beyond 2016 are projections of patients receiving ART based on assumptions in the text. Columns from 2016 to 2021 indicate projected number of patients receiving ART stratified by mode of infection, assuming no improvement in ART uptake or retention. Dashed line from 2016 to 2021 indicates projected numbers on ART assuming a 90% annual rate of retention. Dashed line from 2016 to 2021 indicates projected number of patients receiving ART, assuming 90% uptake of ART and 90% annual rate of retention. ART=antiretroviral therapy.

survive into adolescence without paediatric ART. Successful implementation of PMTCT has led to a large overall decrease in perinatally infected children. Increases in adolescents aged 15–19 years entering care and accessing ART are driven by two distinct groups: those entering care younger than 15 years (probably perinatally infected children who have survived into adolescence),

and those entering care at 15 years or older. The increases in this group (15 years or older) are probably influenced by new horizontal infections (reflected in the sharply contrasting gender distribution in the age group and surveys substantiating this age group as having the highest annual incidence rates of HIV in South Africa);³ successful implementation of the 2010 testing campaigns in this age group (although low rates of testing in this age group estimated in surveys would suggest otherwise); or expansion of the coverage of ART in this age group as eligibility thresholds for initiation of ART have increased.

However, these successes should not overshadow the persistent high incidence of sexual transmission of HIV in adolescent girls, which has also contributed to the increase in adolescent treatment. Most patients in all age groups were female, including 88% of patients entering care at age 15–19 years. These results are in keeping with increased risk of vertical transmission of HIV for female infants^{19,20} and patterns of horizontal transmission already described in the 2017 Human Sciences Research Council survey³ and elsewhere in sub-Saharan Africa,^{21,24} where young women have a higher incidence of HIV than do young men. The difference in incidence between girls and boys is probably a composite of change in incidence in these groups, differences in access to testing, and care-seeking behaviour for girls either independently or through pregnancy and PMTCT-related services. There remains an urgent need to address the inequalities in education, sexual and reproductive health, poverty, and

food security that influence a young woman's risk of acquiring HIV, particularly during this key adolescent period, and to ensure that young men who are infected with HIV seek care.

Low rates of ART initiation after care seeking indicate that current models of HIV care are not meeting the unique needs of adolescents. We observed only two-thirds of adolescents aged 15–19 years (presumably horizontally infected) who entered an HIV care programme as having initiated ART by 2016. By contrast, 87% of patients aged 1–14 years (presumably vertically infected) initiated ART after seeking care by 2016, a similar proportion to those described previously in sub-Saharan Africa²⁵ among those seeking care. The proportion of adolescents aged 15–19 years initiating ART did increase sharply during 2013–16, possibly due to corresponding changes in guidelines increasing eligibility thresholds and fast-tracking particular groups onto treatment. Despite this positive increase in patients initiating ART, several persistent factors can negatively contribute to low rates of uptake of ART observed in adolescents aged 15–19 years, including low proportions of individuals being tested (estimated at 50% for female patients and 46% for male patients²⁴—the lowest testing rates for any age group in South Africa), frequent clinic visits to establish and maintain ART, issues of disclosure of HIV status, and increasing responsibilities at home, particularly among those orphaned by HIV.²⁶

Our findings highlight the importance of preparing South Africa's health systems to deliver effective HIV care to rising numbers of adolescents. Several factors will influence the numbers of adolescents accessing HIV care in the coming years. Effective implementation of PMTCT since 2003–04 will result in fewer vertically infected adolescents in the future, and the increase in patients aged 15–19 years in care will begin to slow if increases in HIV testing and ART uptake in adolescents begin to slow, either due to saturation or programme failures. If, however, South Africa reaches its 90% targets, our projections indicate that the adolescent population on ART could nearly double in the next 5 years. This expansion could have a powerful impact in breaking HIV transmission chains in adolescents, ultimately leading to lower ART burden. If, however, adolescents continue to be the fastest growing group of people living with HIV, while also the least likely to start ART promptly and therefore fall behind on progress towards the goal of providing ART to 90% of those diagnosed with HIV, achieving the full targets nationally in South Africa remains unlikely. Health systems should be assessed as to how the unmet needs of adolescents, particularly those who are horizontally infected, could be addressed through interventions in service delivery in this growing population. Differentiated models of care have shown promise in improving outcomes for adolescents living with HIV,^{27,28} and interventions should be considered to increase uptake

of testing and treatment encompassing both facility-based testing and self-testing, as well as provision of adolescent-friendly services such as youth clubs and convenient clinic times.

Although our analysis is the largest to date investigating South African adolescents in HIV care, there are some limitations that should inform the interpretation of these results. First, although extensively validated record linkage techniques were used, the process could still lead to errors in patient matching so incorrect links might have been made (ie, overmatching) or actual links might have been missed (ie, undermatching). In attempts to quantify the extent of overmatching or undermatching, we validated the linkage algorithm relative to a representative sample of manually coded data and relative to national ID numbers available for a small, non-representative proportion of laboratory specimens. The algorithm had high sensitivity (94%) and positive predictive value (99%) relative to the manually matched quasi-gold standard and 99% sensitivity relative to national ID numbers, when available.¹³ Second, our definitions of events in the care cascade are not based on actual clinical visit dates, but rather are inferred from routine laboratory testing protocols. As such, a patient whose blood samples were not taken or not processed would not be observed in our dataset. The likelihood of such underestimation of those in care and receiving ART might vary by facility type and age group (eg, lower tier facilities with fewer skilled paediatric staff might report lower coverage of routine blood sampling). Third, we did not directly observe mode of transmission. Although our data supported the age of 15 years as a reasonable cutoff to distinguish between sexual and perinatal modes of transmission, horizontal infections before age 15 years would be misclassified as presumably vertically infected in this analysis. Finally, there are some groups not observed directly in the data presented here. In particular, we do not report on laboratory results of infants younger than 1 year, patients accessing care in the private sector, laboratory monitoring done outside of the NHLS on patients who migrate into or out of the South African public sector HIV care programme, and, of course, those who do not test and do not enter the treatment programme. In addition, KwaZulu-Natal is not observed before 2011. However, the proportions observed initiating ART by age category and mode of transmission do not change substantively with the inclusion of the data from KwaZulu-Natal (table 3).

Despite these limitations, the analysis has several strengths. First, the NHLS database is national in scope, covering all children and adolescents seeking care in the public sector HIV programme with a CD4 cell count or viral load test. Second, the laboratory data are high quality. The data come directly from NHLS and do not depend on facility staff copying results into patient charts, nor on research staff extracting data from charts—both of which are

opportunities for data loss and error. Third, record linkage process used to construct the NHLS National HIV Cohort occurs at a national level (ie, not just districts or clinics), leading to far greater deduplication than other available datasets. Because all laboratory tests are observed for individual patients regardless of where they seek care, the dataset is robust to so-called silent transfers in which a patient's undocumented transfer to another facility results in potential double-counting and misclassification of the patient's status, recorded as lost to follow-up at the original facility and a new initiate at the receiving facility. Fourth, the cohort enables identification of key steps of the cascade, including entry to care of non-ART initiators, who are often excluded from existing datasets. As we were able to observe the first CD4 cell count or viral load test recorded in the database regardless of whether the patient returned for care, we could quantify the population entering care independent of retention in care thereafter and probabilities of being on ART conditional on being in care. Fifth, the longitudinal dimension of the cohort enabled identification of the age at which patients sought care—regardless of where they sought care within the public sector system—allowing us to infer probable route of transmission, something previous studies have not been able to do at scale. Sixth, the ability to observe the exact age of the patient at each laboratory sample allowed for finer stratification by age group: we could observe those aged 15–19 years, a group highly pertinent to the adolescent population in South Africa but not reported on directly in the District Health Information Software datasets.

Large-scale HIV treatment for adolescents is an important priority in South Africa. Adolescent treatment programmes are forecast to grow in the future, highlighting the need to prepare for this high priority population. Programmes and interventions directly addressing the unique social and developmental challenges faced by adolescents should be prioritised. Increasing testing and ART uptake in adolescents will be crucial to meeting the South African 90% targets, breaking transmission cycles, and reaching epidemic control.

Contributors

MM, MPF, JB, WM, and SC designed the study. JB, WM, SC, and GS collected data. MM and JB did data analysis. MM, MPF, JB, WM, and SC acquired funding. MM, MPF, JB, and WM did data interpretation. MM and MPF were responsible for supervision. GS, JB, and WM were responsible for validation. MM wrote the original draft. All authors reviewed and edited the text.

Declaration of interests

We declare no competing interests.

Data sharing

Access to primary data is subject to restrictions owing to privacy and ethics policies set by the South African Government. Requests for access to the data can be made to the National Health Laboratory Services directly (<http://www.aarms.nhls.ac.za>) and require a full protocol submission. Inquiries can be made via the Office of Academic Affairs and Research at the National Health Laboratory Service.

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