Beyond clinical trials: Cross-sectional associations of combination antiretroviral therapy with reports of multiple symptoms and non-adherence among adolescents in South Africa

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Background. Studies investigating symptoms associated with combination antiretroviral therapy (cART) use among adolescents in resource-limited settings are rare beyond clinical trials. Identifying adolescents at risk of non-adherence is imperative for HIV/AIDS programming and controlling the epidemic in this key population.
Objective. To examine which cART regimens were associated with reports of multiple symptoms and past-week non-adherence in a large community-traced sample of HIV-positive adolescents in South Africa (SA).
Methods. A total of 1 175 HIV-positive ART-experienced adolescents aged 10 - 19 years attending 53 health facilities in the Eastern Cape Province, SA, were interviewed in 2014 - 2015. Ninety percent (*n*=1 059) were included in the study. Adolescents who reported no medication use and those with unclear or missing data were excluded from further analysis, resulting in a sample for analysis of *n*=501. Outcomes were reports of multiple symptoms (three or more symptoms in the past 6 months) and past-week ART non-adherence (<95% correct doses in the past week). Multivariable logistic regression analyses controlled for sociodemographic and HIV-related covariates in Stata 13/IC.
Results. Of the adolescents included, 54.3% were female. The median age was 14 (interquartile range 12 - 16) years, and 66.5% were vertically infected. The prevalence of multiple symptoms was 59.7% (95% confidence interval (CI) 55.3 - 63.9). Independent of covariates, stavudine (d4T)-containing cART regimens and the fixed-dose combination of tenofovir (TDF) + emtricitabine (FTC) + efavirenz (EFV) were associated with more reports of multiple symptoms (adjusted odds ratio (aOR) 3.38; 95% CI 1.19 - 9.60 and aOR 2.67; 95% CI 1.21 - 5.88, respectively). Lopinavir/ritonavir (LPV/r)-containing regimens were associated with fewer reports of multiple symptoms (aOR 0.47; 95% CI 0.21 - 1.04). For EFV-based regimens, adolescents on d4T + lamivudine (3TC) + EFV were more likely to report multiple symptoms than those on TDF + FTC + EFV or those on abacavir (ABC) + 3TC + EFV (aOR 3.26; 95% CI 1.01 - 10.52, aOR 2.86; 95% CI 1.35 - 6.05 and aOR 1.08; 95% CI 0.64 - 1.82, respectively). However, only TDF + FTC + EFV cART was associated with lower levels of non-adherence among participants (aOR 0.44; 95% CI 0.21 - 0.93).
Conclusions. Rates of multiple symptoms among HIV-positive ART-experienced adolescents were high. d4T-containing regimens and TDF + FTC + EFV were associated with more reports of multiple symptoms, whereas LPV/r-containing regimens were associated with fewer reports. However, adolescents on TDF + FTC + EFV were the most adherent subgroup. These findings support the World Health Organization-recommended discontinuation of d4T use, but also underscore the dilemma faced by clinicians when choosing between low-toxicity regimens and those that promote ART adherence, particularly among HIV-positive adolescents.

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Globally, adolescents aged 10 - 19 years are the only age group in which AIDS-related deaths are increasing, and AIDS is now the leading cause of adolescent death in Africa.[1] Combination antiretroviral therapy (cART) increases long-term survival and wellbeing of people living with HIV,[2] but requires diligent lifetime adherence of ~87 - 95%.[3] However, cART has also been associated with toxicities in clinical trials. Low adherence rates are common among HIV-positive adolescents and rates have been shown to worsen over time,[4,5] but more research is needed to understand what drives adolescent non-adherence to cART, particularly in sub-Saharan Africa. Side-effects of cART are important both with regard to quality of life and as potential predictors of non-adherence. In clinical practice, symptoms associated with cART use and symptoms of opportunistic infections in HIV or other illnesses can easily be confused. Symptoms commonly listed in the literature as side-effects of cART include skin rash, fatigue/tiredness, nausea/vomiting, diarrhoea/stomach ache, insomnia/bad dreams, headache, fever, dry mouth and dizziness.[6-9] Evidence on cART-related symptoms among adolescents is very limited, particularly in sub-Saharan Africa, where a >90-fold increase in cART access has occurred in the past decade.[10] Most studies reporting cART-related outcomes focus on adults or younger children (<14 years) or include very few children.[4,7,11-17]

In younger children, observational studies and randomised controlled trials (RCTs) comparing nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)-based and non-nucleotide reverse transcriptase inhibitor (NNRTI)-based regimens have found no major differences in toxicity profiles,[15,17-19] including in children with prior nevirapine (NVP) exposure.[20] In Uganda, 23% of children aged <18 years reported mild to moderate symptoms, and in Rwanda, 33% of children aged <15 reported cART-related symptoms, 9% of whom required treatment modification. However, these studies did not specify which regimens/regimen components were likely to be associated with the reported symptoms.[8,21] Studies in high-income countries have shown zidovudine (AZT)-based regimens to be safer than stavudine (d4T)-based regimens,[9] and lopinavir/ritonavir (LPV/r)-based regimens to be safe and effective in HIV-infected children.[22,23] Studies in adults report cough, fever, peripheral neuropathy, skin rash, pruritus, diarrhoea and dizziness to be common among participants on AZT- and d4T-based cART, with higher prevalences in participants on AZT-based regimens than in those on d4T-based regimens.[14,24] RCTs and systematic reviews in adults in high-income countries have also shown efavirenz (EFV)-based regimens to be associated with more symptoms than non-EFV-based regimens.[7,25]

To date, no study has examined associations between cART regimens and reports of multiple symptoms among HIV-positive adolescents. Clinical trials of specific medications (which often exclude children and adolescents aged <18 years) may underestimate treatment-associated symptoms because they are conducted in strictly controlled settings and follow participants for only a limited period.

Objective

To examine which cART regimens were associated with reports of multiple symptoms and past-week non-adherence in a large community-traced sample of HIV-positive 10 - 19-year-old adolescents in South Africa (SA). For the purposes of the study, multiple symptoms were defined as reports of three or more symptoms in the past 6 months and non-adherence as <95% of prescribed doses taken correctly in the past week.

Methods

This was a cross-sectional study conducted with HIV-positive adolescents aged 10 - 19 years, resident in a mixed urban, periurban and rural health district of Amathole (area 21 117 km^2, total population 880 790),[26,27] Eastern Cape – SA's poorest province, with an antenatal HIV prevalence of 29.1% (95% confidence interval (CI) 27.3 - 30.9).[28] ART-providing public health facilities that reported four or more adolescents on treatment in the study area were selected (N=53). All ART-experienced adolescents in these healthcare facilities were identified (N=1 175 eligible) and then followed up in their homes (community tracing) to enable participant inclusion regardless of clinic attendance status (active or lost to follow-up). Reasons for non-participation were as follows: caregiver or adolescent refused (4.1%), severe cognitive delays (0.9%), untraceable (3.7%) and not interviewed for safety reasons (1.2%). Of the eligible sample, 90.1% (n=1 059) of ART-experienced adolescents were interviewed alongside 467 community controls, 10 - 19-year-old adolescents who were either living in the same home or a neighbouring home.

Research tools were translated and back-translated from English into Xhosa and piloted with 25 HIV-positive adolescents. Adolescents used their preferred language. Interviewers were trained in conducting research with HIV-affected adolescents. To prevent stigmatisation of participants and unintended disclosure, the study was presented within communities and organisations as investigating adolescent health service needs. Confidentiality was maintained, except when participants requested assistance or were at risk of significant harm. In cases of self-reported abuse, rape or risk of significant harm, adolescents were referred to child protection and health services with follow-up support where needed. Voluntary informed consent was obtained from all adolescents aged ≥18 years, and assent was obtained from those aged <18, with their caregivers providing consent. There were no incentives provided, but participants received a pack containing a snack, a toothbrush, toothpaste, and a certificate of participation.

Ethics approval

Ethical clearance was obtained from the relevant academic institutions (the universities of Oxford (ref. no. SSD/CUREC2/12-21) and Cape Town (ref. no. CSSR 2013/4)), governmental organisations (the Eastern Cape departments of Health and Basic Education), and ethical review boards of participating health facilities.

Measures

The adolescents' knowledge of their own HIV status was determined from clinic records and healthcare worker and primary caregiver reports. Owing to discrepancies between these sources, it was imperative to check that adolescents understood their HIV status to prevent unintentional disclosure through research.[29,30] Adolescents were asked about whether they knew what their illness was, whether they had ever been tested for HIV and whether they knew what their medication was for. Those who reported not knowing their status were asked about 'illness' and 'medication' instead of 'HIV' and 'ART' throughout the study.

Symptoms were assessed using the verbal symptoms scale.[31] Adolescents were asked about a range of symptoms and how frequently (never, sometimes, often) they had experienced them in the past 6 months. Anxiety was assessed using a pro-rated version of the revised children's manifest anxiety scale (RCMAS).[32]

Treatment information was obtained by asking adolescents to state the names of their current medication where known, or say 'I don't know' if unknown. Participant responses were entered as free text in the dataset by the interviewer. Given the unreliability of clinical records in resource-limited settings, a photograph of their current medication was taken by the interviewer where possible. **ART and other medication variables** were generated from textual and photographic medication data and coded using the 2015 SA national ART guidelines,[6] corroborated by the 2015 World Health Organization (WHO)[33] and National Institutes of Health ART guidelines,[34] and through consultations with paediatric ART expert clinicians and nurse practitioners. Individual ART variables were then combined into specific cART regimens and broader groups of NRTI-, NNRTI- and protease inhibitor (PI)-containing regimens in accordance with the 2015 SA national ART guidelines,[6] expert clinician guidance and precedent studies.[15,17,25] For example, if the adolescents' textual or photographic responses included abacavir (ABC), they were coded as 1 on a dummy variable for ABC-based regimens. If the responses included multiple medicines, these were recoded in individual dummy variables. Where brand names were used, for example Erige for EFV, Kaletra or Aluvia for ritonavir-boosted LPV and Atripla for the fixed-dose combination TDF + emtricitabine (FTC) + EFV, expert clinicians were consulted to assign standard medicine codes. Combination ART variables were generated in accordance with the 2015 SA national ART guidelines[6] and the 2015 WHO guidelines.[33] For example, adolescents were coded on the ABC + lamivudine (3TC) +EFV combination regimen if they had three dummy variables from their textual and/or photographic

responses for ABC, 3TC and EFV. Higher-level ART variables were generated as follows: participants were positively coded for NNRTI-based regimens if they were on a regimen containing either EFV or NVP, for NRTI-based regimens if they were on a regimen containing either ABC or tenofovir (TDF) or d4T or AZT, and for PI-based regimens if they were on a regimen containing LPV/r, darunavir-ritonavir (DRV/r), atazanavir (ATV), raltegravir or DRV/retravirine.

Past-week ART non-adherence was defined as <95% correct doses in the past week[35] and assessed by adolescent self-report[36,37] based on items from the standardised Patient Medication Adherence Questionnaire[38] combined with measures developed in Botswana.[39] Adolescent past-week ART non-adherence in this study has already been validated using patient file viral load (VL) data and self-reported opportunistic infections.[5,40]

Potential covariates included sociodemographic, health and wellbeing/HIV-related and healthcare-related factors. **Socio-demographics** of adolescent age, sex, language, urban/rural residence and formal/informal housing were measured using items adapted from the 2011 South African census.[41] Poverty, defined in this study as lacking all the eight socially perceived necessities for children, was measured using an index of household assets corroborated by 80% of the population in a nationally representative survey.[42] Food insecurity was measured using items from the SA National Food Consumption Survey[43] and was defined as spending 2 or more days in the past week without sufficient food. **HIV-related factors** included positive status knowledge, VL, CD4+ count, opportunistic infections and mode of infection (vertical/horizontal). Recent CD4+ and VL data were extracted from patient files and the Tier.Net database after obtaining approval from participants and administrators at participating clinics. Suboptimal immunity was defined as a CD4+ count <500 cells/μL, based on the WHO 2013 ART treatment guidelines.[44] Recent treatment failure was defined as VL >1 000 copies/mL.[19] **Opportunistic infections,** defined as reporting sores on the body or face, tuberculosis (TB) or mouth ulcers in the past 6 months, were assessed using a verbal symptom scale. Using data from similar studies in SA, adolescents were classed as **vertically infected** if they had started ART before age 12 years or if they had been on treatment for >5 years.[45] **Overall health** (excellent/not excellent) and **medication cofactors** of age at ART initiation, daily pill burden, medication frequency, antibiotics/TB medication and past-year ART stock-outs were recorded through adolescent self-report. **Time on treatment** was calculated as the difference between adolescent age and age at ART initiation. **Healthcare cofactors** linked with non-adherence included clinic transport problems (at least one negative experience related to transport), clinic staff problems (>3 negative clinic staff-related experiences), and clinic facility problems (>3 negative facility- or accessibility-related experiences).

Data analysis

Of the included HIV-positive sample (*n*=1 059), adolescents with unclear or missing information (31.5%) and those who stated no current medication use, including defaulters (21.2%), were excluded from subsequent analyses (*n*=558, 53.0%), generating a final sample for analysis of *n*=501. Adolescent ART self-reports were validated using patient file data at participating clinics and the Tier.net database, using a subsample (*n*=194, 38.7%) of participants.

Analyses were conducted in five stages in SPSS version 22 (IBM, USA) and Stata version 13.0/IC (StataCorp, USA). First, to check for potential differences between the included and excluded participants, the two groups were compared on known characteristics. Subgroup differences in medians and proportions were assessed using the median command and a series of χ^2 tests, respectively (Table 1). Second, we described the baseline sociodemographic, health and wellbeing characteristics of the included sample (Table 2). Third, a literature-based strategy was used to determine common medication symptoms.[6,46,47] We assessed the distribution of symptoms between HIV-positive adolescents and community controls (apparently HIV-negative adolescents) and eliminated symptoms that were not differentially distributed between the two groups (headache, fever and backache; results available on request). The final ten symptoms that were analysed as potentially ART-associated were ear problems, skin rash, diarrhoea, nausea/vomiting, stomach problems, dizziness, problems sleeping/bad dreams, tiredness, weight loss and clinical anxiety (scores >9 on a pro-rated RCMAS). Our study aimed to identify severely affected adolescents (a clinically important group), so the major outcome – **multiple symptoms** – was computed as reports of ≥3 symptoms in the past 6 months.

Fourth, associations of cART regimens with multiple symptoms were tested in multivariate logistic regressions using a subsample of 468 (93.4%) HIV-positive ART-experienced adolescents who had complete data for all the included variables. Analyses controlled for potential confounders of age, gender, rural residence, overall

Table 1. Comparison of known baseline characteristics of included and excluded adolescents in the study (*N*=1 059)

Characteristic	Included (*N*=501)	Excluded (*N*=558)	χ^2	*p*-value‡
Age (yr), median (IQR)†	14 (12 - 16)	13 (11 - 16)	16.133	<0.001*
Girls, *n* (%)	272 (54.3)	311 (55.7)	0.222	0.637
Rural, *n* (%)	98 (19.4)	129 (23.3)	2.161	0.142
Informal housing, *n* (%)	88 (17.6)	111 (19.9)	0.937	0.333
Food insecurity, *n* (%)	62 (12.4)	91 (16.3)	3.348	0.067*
Past-month poor health, *n* (%)	211 (42.1)	223 (40.0)	0.505	0.477
Perinatally infected, *n* (%)	333 (66.5)	375 (67.2)	0.065	0.799
Time on treatment (years), median (IQR)†	5 (2 - 9)	5 (2 - 10)	0.018	0.892
Pill burden (≥5/day), *n* (%)	260 (51.9)	280 (52.0)	0.002	0.962
Daily dosing frequency ≥2, *n* (%)	240 (47.9)	246 (45.7)	0.495	0.482
≥3 self-reported symptoms, *n* (%)	299 (59.7)	349 (62.7)	0.985	0.321
Past-week non-adherence, *n* (%)	149 (29.7)	236 (42.3)	17.989	<0.001*
Any opportunistic infections, *n* (%)	298 (59.5)	333 (59.7)	0.004	0.948

IQR = interquartile range.
*Significant at $p<0.1$.
†Continuous variables were skewed and could not be transformed successfully, so medians (IQR) are presented.
‡*p*-values are from median tests for continous variables and from χ^2 tests for categorical variables.

Table 2. Characteristics of adolescents included in the study (*N*=501)

Characteristic	*n* (%)	95% CI	Median (IQR)
Sociodemographic variables			
Overall age (yr)*			14 (12 - 16)
10 - 14	282 (56.3)	51.9 - 60.6	
15 - 19	219 (43.7)	39.4 - 48.1	
Xhosa language	488 (97.4)	95.6 - 98.5	
Girls	272 (54.3)	49.9 - 58.6	
Rural residence	98 (19.6)	16.3 - 23.3	
Informal housing	88 (17.6)	14.5 - 21.2	
Poverty (lacked access to basic necessities)	338 (67.5)	63.2 - 71.4	
Food insecurity	62 (12.4)	9.8 - 15.6	
Orphanhood (any)	303 (60.5)	56.1 - 64.7	
Health and wellbeing variables			
Excellent health (no)	290 (57.9)	53.5 - 62.2	
Knows HIV status (yes)	427 (85.2)	81.8 - 88.1	
Perinatally infected	333 (66.5)	62.2 - 70.5	
Self-reported symptoms			
≥3 self-reported symptoms	299 (59.7)	55.3 - 63.9	
Shingles/skin rash	223 (44.5)	40.2 - 48.9	
Diarrhoea	219 (43.7)	39.4 - 48.1	
Nausea/vomiting	217 (43.3)	39.0 - 47.7	
Tires easily	211 (42.1)	37.9 - 46.5	
Stomach problems	202 (40.3)	36.1 - 44.7	
Dizziness	167 (33.3)	29.3 - 37.6	
Ear problems	160 (31.9)	28.0 - 36.2	
Bad dreams/insomnia	149 (29.7)	25.9 - 33.9	
Weight loss	131 (26.2)	22.5 - 30.2	
Anxiety (above clinical cut-off)	12 (2.4)	1.4 - 4.2	
Medication variables			
Number of ARVs, median (IQR)*			3 (1 - 3)
One ARV	180 (35.9)	31.8 - 40.2	
≥2 ARVs	321 (64.1)	59.8 - 68.2	
≥5 pills/day	260 (51.9)	47.5 - 56.3	
Daily dosing frequency ≥2	240 (47.9)	43.5 - 52.3	
Antibiotics, including TB medication	70 (14.0)	11.2 - 17.4	
EFV-based regimens	354 (70.7)	66.5 - 74.5	
LPV/r-based regimens	85 (17.0)	13.9 - 20.5	
3TC-based regimens	322 (64.3)	41.6 - 48.6	
ABC-based regimens	231 (46.1)	41.8 - 50.5	
TDF-based regimens	143 (28.5)	24.8 - 32.7	
AZT-based regimens	51 (10.2)	7.8 - 13.2	
D4T-based regimens	32 (6.4)	4.5 - 8.9	
NVP-based regimens	3 (0.6)	0.2 - 1.9	
3TC monotherapy	38 (7.6)	5.6 - 10.3	
TDF + FTC + EFV	116 (23.2)	19.7 - 27.1	
ABC + 3TC + EFV	165 (32.9)	28.9 - 37.2	
Past week non-adherence	149 (29.7)	25.9 - 33.9	
Time on treatment (yr)*			5 (2 - 10)

CI = confidence interval; IQR = interquartile range; ARV/s = antiretroviral/s; TB = tuberculosis; EFV = efavirenz; LPV/r = lopinavir/ritonavir; 3TC = lamivudine; ABC = abacavir; TDF = tenofovir; AZT = zidovudine; d4T = stavudine; FTC = emtricitabine.
*Continuous variables were skewed and could not be transformed successfully, so medians (IQR) are presented.

health status, food insecurity, lacking all the eight basic necessities, antibiotics/TB medication, pill burden (≥5), daily dosing frequency (≥2), past-week non-adherence, CD4+ count (<500 cells/μL), recent treatment failure (VL >1 000 copies/mL), opportunistic infections, ART stock-outs, vertical infection and time on treatment. Separate models (Tables 3, 4, 5 and 6) were run as follows: (*i*) comparing NRTI-based regimens (ABC-containing v. AZT-containing v. TDF-containing v. d4T-containing regimens); (*ii*) comparing TDF + FTC + EFV v. other EFV-containing regimens; (*iii*) comparing NNRTI-based v. PI-based (EFV-containing v. LPV/r-containing regimens); and (*iv*) comparing EFV-based regimens (D4T + 3TC + EFV v. TDF + FTC + EFV v. ABC + 3TC + EFV). In the latter model, ABC +

Table 3. Comparing NRTI-based cART regimens, all potential covariates simultaneously added to the model (*N*=468)

	Outcome ≥3 self-reported symptoms	
Exposure variables	**aOR (95% CI)**	***p*-value**
AZT-containing regimens (Y/N)	0.73 (0.35 - 1.52)	0.393
ABC-containing regimens (Y/N)	0.94 (0.53 - 1.67)	0.820
TDF-containing regimens (Y/N)	1.50 (0.71 - 3.21)	0.291
D4T-containing regimens (Y/N)	3.38 (1.19 - 9.60)	0.022*
Age	0.96 (0.85 - 1.09)	0.533
Female gender (Y/N)	1.24 (0.80 - 1.93)	0.343
Rural residence (Y/N)	0.76 (0.47 - 1.29)	0.300
Past-month poor health (Y/N)	2.37 (1.53 - 3.68)	<0.001*
Food insecurity (Y/N)	2.03 (0.99 - 4.15)	0.052*
Lack access to basic necessities (Y/N)	1.22 (0.76 - 1.95)	0.405
Antibiotics/TB treatment (Y/N)	1.83 (0.93 - 3.57)	0.079*
Past-week non-adherence (Y/N)	1.16 (0.72 - 1.87)	0.538
≥5 pills/day (Y/N)	1.18 (0.72 - 1.95)	0.513
Daily dosing frequency ≥2 (Y/N)	0.96 (0.59 - 1.57)	0.881
Past-year ARV stock-outs (Y/N)	0.67 (0.59 - 1.57)	0.408
Recent CD4+ <500 cells/μL (Y/N)	1.37 (0.64 - 2.95)	0.415
Recent treatment failure/VL >1 000 copies/mL (Y/N)	0.85 (0.31 - 2.31)	0.748
Any opportunistic infections (Y/N)	4.64 (2.98 - 7.21)	<0.001*
Vertical infection (Y/N)	0.76 (0.35 - 1.69)	0.505
Time on treatment	0.98 (0.92 - 1.04)	0.506

NRTI = nucleos(t)ide reverse transcriptase inhibitor; cART = combination antiretroviral therapy; AZT = zidovudine; ABC = abacavir; TDF = tenofovir d4T = stavudine; aOR = adjusted odds ratio; CI = confidence interval; Y = yes; N = no; TB = tuberculosis; ARV = antiretroviral; VL = viral load.
*Effects significant at $p<0.1$.

Table 4. Comparing TDF + FTC + EFV with other EFV-based regimens, all potential covariates simultaneously added to the model (*N*=468)

	Outcome ≥3 self-reported symptoms	
Exposure variables	**aOR (95% CI)**	***p*-value**
TDF + FTC + EFV (Y/N)	2.67 (1.21 - 5.88)	0.015*
Other EFV-based† cART (Y/N)	1.11 (0.67 - 1.84)	0.694
Age	0.95 (0.85 - 1.06)	0.348
Female gender (Y/N)	1.17 (0.76 - 1.82)	0.479
Rural residence (Y/N)	0.77 (0.46 - 1.32)	0.344
Past-month poor health (Y/N)	2.24 (1.45 - 3.46)	<0.001*
Food insecurity (Y/N)	1.85 (0.91 - 3.77)	0.090*
Lack access to basic necessities (Y/N)	1.26 (0.79 - 2.00)	0.340
Antibiotics/TB treatment (Y/N)	1.74 (0.89 - 3.38)	0.106
Past-week non-adherence (Y/N)	1.20 (0.74 - 1.93)	0.457
≥5 pills/day (Y/N)	1.25 (0.76 - 2.04)	0.386
Daily dosing frequency ≥2 (Y/N)	1.08 (0.67 - 1.76)	0.749
Past-year ARV stock-outs (Y/N)	0.72 (0.28 - 1.86)	0.501
Recent CD4+ <500 cells/μL (Y/N)	1.43 (0.66 - 3.07)	0.365
Recent treatment failure/VL >1 000 copies/mL (Y/N)	1.00 (0.37 - 2.71)	0.991
Any opportunistic infections (Y/N)	4.66 (3.01 - 7.22)	<0.001*
Vertical infection (Y/N)	0.76 (0.35 - 1.68)	0.499
Time on treatment	0.98 (0.93 - 1.05)	0.599

TDF = tenofovir; FTC = emtricitabine; EFV = efavirenz; aOR = adjusted odds ratio; CI = confidence interval; Y = yes; N = no; cART = combination antiretroviral therapy; TB = tuberculosis; ARV = antiretroviral; VL = viral load.
*Effects significant at $p<0.1$.
†All EFV-containing regimens excluding TDF + FTC + EFV.

3TC + EFV, being the largest of the three EFV-based regimens, was selected as the reference category. Covariates were simultaneously added to each model. Predicted probabilities of reporting multiple symptoms were computed for all major cART regimens in marginal-effects models, adjusted for all covariates held at their mean values. Associations between cART regimens and individual symptoms were also explored and presented (Table 7). Low-frequency ART regimens ($n<20$ adolescents) were excluded from analyses.

Fifth, we assessed which cART regimens (only those significant in stage 4 above) were associated with adolescent self-reported non-adherence (past week), adjusted for several covariates including multiple symptoms (Table 8).

Table 5. Comparing PI-based with NNRTI-based regimens, all potential covariates simultaneously added to the model (*N*=468)

	Outcome ≥3 self-reported symptoms	
Exposure variables	**aOR (95% CI)**	***p*-value**
LPV/r-containing regimens (Y/N)	0.47 (0.21 - 1.04)	0.061*
EFV-containing regimens (Y/N)	0.86 (0.45 - 1.65)	0.651
Age	1.00 (0.90 - 1.11)	0.959
Female gender (Y/N)	1.16 (0.78 - 1.83)	0.465
Rural residence (Y/N)	0.74 (0.43 - 1.25)	0.258
Past-month poor health (Y/N)	2.34 (1.52 - 3.61)	<0.001*
Food insecurity (Y/N)	1.95 (0.96 - 3.95)	0.063*
Lack access to basic necessities (Y/N)	0.81 (0.51 - 1.29)	0.375
Antibiotics/TB treatment (Y/N)	1.75 (0.90 - 3.40)	0.100
Past-week non-adherence (Y/N)	1.12 (0.70 - 1.81)	0.634
≥5 pills/day (Y/N)	1.11 (0.71 - 1.75)	0.639
Daily dosing frequency ≥2 (Y/N)	1.13 (0.68 - 1.87)	0.636
Past-year ARV stock-outs (Y/N)	0.69 (0.26 - 1.79)	0.441
Recent CD4+ <500 cells/μL (Y/N)	1.42 (0.67 - 3.04)	0.363
Recent treatment failure/VL >1 000 copies/mL (Y/N)	0.85 (0.32 - 2.23)	0.734
Any opportunistic infections (Y/N)	4.44 (2.87 - 6.86)	<0.001*
Vertical infection (Y/N)	0.75 (0.34 - 1.65)	0.473
Time on treatment	0.98 (0.92 - 1.04)	0.487

PI = protease inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; LPV/r = ritonavir-boosted lopinavir; EFV = efavirenz; aOR = adjusted odds ratio; CI = confidence interval; Y = yes; N = no; TB = tuberculosis; ARV = antiretroviral; VL = viral load.
*Effects significant at $p<0.1$.

Table 6. Associations between EFV-containing regimens and multiple symptoms, all potential covariates simultaneously added to the model (*N*=468)

	Outcome ≥3 self-reported symptoms	
Exposure variables	**aOR (95% CI)**	***p*-value**
D4T + 3TC + EFV (Y/N)	3.26 (1.01 - 10.52)	0.048*
TDF + FTC + EFV (Y/N)	2.86 (1.35 - 6.05)	0.006*
ABC + 3TC + EFV (Y/N)	1.08 (0.64 - 1.82)	0.784
Age	0.94 (0.83 - 1.05)	0.255
Female gender (Y/N)	1.19 (0.77 - 1.85)	0.429
Rural residence (Y/N)	0.78 (0.46 - 1.33)	0.362
Past-month poor health (Y/N)	2.27 (1.47 - 3.51)	<0.001*
Food insecurity (Y/N)	1.94 (0.94 - 3.97)	0.071*
Lack access to basic necessities (Y/N)	1.24 (0.77 - 1.98)	0.373
Antibiotics/TB treatment (Y/N)	1.80 (0.92 - 3.54)	0.086*
Past-week non-adherence (Y/N)	1.22 (0.75 - 1.98)	0.424
≥5 pills/day (Y/N)	1.26 (0.76 - 2.10)	0.365
Daily dosing frequency ≥2 (Y/N)	1.06 (0.66 - 1.73)	0.805
Past-year ARV stock-outs (Y/N)	0.69 (0.27 - 1.79)	0.444
Recent CD4+ <500 cells/μL (Y/N)	1.41 (0.65 - 3.04)	0.383
Recent treatment failure/VL >1 000 copies/mL (Y/N)	0.91 (0.33 - 2.50)	0.860
Any opportunistic infections (Y/N)	4.66 (3.00 - 7.25)	<0.001*
Vertical infection (Y/N)	0.76 (0.34 - 1.67)	0.491
Time on treatment	0.98 (0.93 - 1.05)	0.582

EFV = efavirenz; D4T = stavudine; 3TC = lamivudine; TDF = tenofovir; FTC = emtricitabine; ABC = abacavir; aOR= adjusted odds ratio; CI = confidence interval; Y = yes; N = no; TB = tuberculosis; ARV = antiretroviral; VL = viral load.
*Effects significant at $p<0.1$.

Results

Sociodemographic, health and wellbeing characteristics of the study population

Community controls were demographically similar to HIV-positive adolescents in many sociodemographic characteristics except for age and gender. The controls were significantly older than the HIV-positive adolescents, with a median age of 15 (interquartile range (IQR) 12 - 17) years v. 13 (IQR 11 - 16) years; $p<0.001$) and a comparatively higher proportion were girls, 60.8% v. 55.1%; $p=0.036$). Of the controls ($n=467$), 94.0% were Xhosa-speaking, 76.2% were urban dwellers, 84.4% lived in formal housing, and 63.6% lacked access to basic necessities (results not presented). Compared with those included in the study, excluded adolescents were significantly younger (median age difference 1 year; $p<0.001$), and reported higher rates of food insecurity (proportional difference 3.9%; $p=0.067$) and higher rates of past-week non-adherence (proportional difference

Table 7. Associations of various cART regimens with selected symptoms among 10 - 19-year-old HIV-positive ART-experienced adolescents in SA (*N*=501)†

ART category	Ear problems (*n*=160)	Skin rash (*n*=223)	Diarrhoea (*n*=219)	Nausea/ vomiting (*n*=217)	Stomach problems (*n*=202)	Dizziness (*n*=167)	Sleep problem/ bad dreams (*n*=149)	Tiredness (*n*=211)	Weight loss (*n*=131)	Clinical anxiety (*n*=12)
Common cART regimen										
ABC + 3TC + EFV (*n*=165)	0.87 (0.53 - 1.45)	**0.61** (0.38 - 0.99)**	**0.58** (0.35 - 0.94)**	1.10 (0.68 - 1.79)	1.01 (0.62 - 1.65)	**1.92** (1.12 - 3.27)**	**1.33** (0.80 - 2.21)	0.98 (0.60 - 1.59)	**0.80** (0.46 - 1.41)	**0.49** (0.02 - 9.90)
TDF + FTC + EFV (*n*=116)	1.11 (0.57 - 2.18)	**1.50** (0.78 - 2.91)	**1.45** (0.75 - 2.80)	0.97 (0.50 - 1.88)	**1.64** (0.85 - 3.18)	**1.37** (0.69 - 2.67)	**1.64** (0.82 - 3.29)	**1.40** (0.73 - 2.68)	0.99 (0.48 - 2.03)	**2.77** (0.24 - 31.0)
d4T + 3TC + EFV (n=22)	1.06 (0.39 - 2.86)	**0.58** (0.21 - 1.58)	**1.25** (0.48 - 3.30)	**1.93** (0.73 - 5.10)	**1.20** (0.46 - 3.16)	0.96 (0.34 - 2.71)	0.95 (0.34 - 2.66)	**1.74** (0.65 - 4.62)	0.85 (0.29 - 2.51)	**23.2** (1.48 - 362.8)**
ABC + AZT + LPV/r (*n*=22)	**1.28** (0.46 - 3.58)	**2.23** (0.81 - 6.18)	**0.68** (0.25 - 1.89)	**0.34** (0.11 - 1.04)*	**1.68** (0.59 - 4.75)	**0.76** (0.25 - 2.34)	**0.59** (0.18 - 1.91)	0.91 (0.33 - 2.58)	**1.69** (0.58 - 4.89)	**1.65** (0.03 - 95.4)
ABC + 3TC + LPV/r (*n*=18)	1.05 (0.36 - 3.02)	1.13 (0.40 - 3.15)	1.02 (0.36 - 2.92)	0.89 (0.31 - 2.51)	**0.67** (0.21 - 1.96)	**0.09** (0.01 - 0.72)**	**0.79** (0.25 - 2.45)	1.09 (0.38 - 3.13)	**0.64** (0.18 - 2.26)	§
AZT + 3TC + LPV/r (*n*=14)	1.07(0.29 - 3.91)	**2.08** (0.64 - 6.76)	**2.08** (0.64 - 6.76)	1.02 (0.31 - 3.38)	**0.90** (0.27 - 2.99)	0.93 (0.24 - 3.53)	**1.45** (0.43 - 4.86)	**2.45** (0.74 - 8.13)	**1.73** (0.44 - 6.32)	**3.74** (0.11 - 122.5)
NRTI-containing regimen										
D4T based (*n*=32)	0.87 (0.37 - 2.04)	**0.58** (0.25 - 1.35)	**1.57** (0.71 - 3.48)	**2.47** (1.09 - 5.62)**	**1.41** (0.63 - 3.16)	**0.77** (0.32 - 1.88)	1.19 (0.52 - 2.72)	**3.09** (1.34 - 7.11)***	**1.44** (0.60 - 3.42)	**11.0** (0.77 - 156.1)
TDF based (*n*=143)	**0.78** (0.41 - 1.47)	1.17 (0.63 - 2.17)	1.07 (0.58 - 1.99)	1.14 (0.61 - 2.13)	1.04 (0.55 - 1.94)	0.82 (0.43 - 1.56)	1.10 (0.58 - 2.12)	**0.75** (0.41 - 1.40)	1.10 (0.56 - 2.15)	**0.79** (0.10 - 6.57)
ABC based (*n*=231)	1.15 (0.69 - 1.91)	**0.65** (0.40 - 1.05)*	**0.62** (0.38 - 1.01)*	0.99 (0.61 - 1.61)	0.98 (0.60 - 1.60)	1.11 (0.66 - 1.88)	1.10 (0.66 - 1.83)	0.94 (0.58 - 1.53)	**0.67** (0.38 - 1.17)	**1.47** (0.09 - 24.7)
AZT based (*n*=51)	**1.70** (0.84 - 3.44)	**1.38** (0.70 - 2.72)	1.01 (0.51 2.00)	**0.58** (0.28 - 1.18)	0.97 (0.48 - 1.97)	0.91 (0.43 - 1.93)	0.85 (0.41 - 1.79)	**1.20** (0.60 - 2.40)	**1.24** (0.58 - 2.64)	**1.31** (0.09 - 19.7)
NNRTI-containing regimen										
All EFV based (*n*=354)	0.95 (0.58 - 1.54)	**0.80** (0.50 - 1.27)	0.86 (0.54 - 1.37)	**1.27** (0.79 - 2.04)	1.17 (0.73 - 1.90)	**1.83** (1.09 - 3.08)**	**1.58** (0.95 - 2.65)*	0.93 (0.58 - 1.48)	0.85 (0.50 - 1.45)	**0.67** (0.08 - 5.40)
Other EFV based (*n*=239)‡	0.90 (0.57 - 1.42)	**0.67** (0.43 - 1.04)*	**0.68** (0.44 - 1.05)	**1.25** (0.83 - 2.00)	0.90 (0.58 - 1.41)	**1.53** (0.95 - 2.46)*	**1.23** (0.78 - 1.98)	0.83 (0.53 - 1.29)	0.87 (0.53 - 1.43)	**0.40** (0.06 - 2.52)
PI-containing regimen										
LPV/r based (*n*=85)	1.16 (0.64 - 2.14)	**1.55** (0.87 - 2.76)	1.00 (0.57 - 1.80)	**0.53** (0.29 - 0.96)**	**0.64** (0.36 - 1.19)	**0.39** (0.19 - 0.77)***	**0.70** (0.37 - 1.31)	1.08 (0.60 - 1.93)	0.86 (0.45 - 167)	0.91 (0.08 - 10.0)
3TC holding/monotherapy										
On 3TC alone (*n*=38)¶	0.82 (0.36 - 1.87)	1.17 (0.54 - 2.56)	**1.33** (0.60 2.93)	0.87 (0.39 - 1.95)	**1.53** (0.69 - 3.40)	**1.38** (0.61 - 3.13)	**0.64** (0.25 - 1.64)	**0.61** (0.26 - 1.41)	**1.38** (0.57 - 3.33)	§

cART = combination antiretroviral therapy; ART = antiretroviral therapy; SA = South Africa; OR = odds ratio; CI = confidence interval; ABC = abacavir; 3TC = lamivudine; EFV = efavirenz; TDF = tenofovir; FTC = emtricitabine; d4T = stavudine; AZT = zidovudine; LPV/r = lopinavir/ritonavir; NRTI = nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; 3TC = lamivudine.
*$p<0.1$; **$p<0.05$; ***$p<0.01$.
†Values are ORs (adjusted for age, gender, rural residence, past-month poor health, food insecurity, lacking access to eight socially perceived basic necessities, antibiotic/TB treatment, past-week non-adherence, pill burden, medication frequency, ART stock-outs, recent CD4+ count, recent treatment failure, opportunistic infections, vertical infection and time on treatment) and 95% CIs. Values in bold are potential hits where a regimen reduces or increases the likelihood of reporting a given symptom by >20%.
‡Excludes TDF + FTC + EFV combination ART.
¶Adolescents on a 3TC holding period before moving to second-line ART.
§Analysis dropped owing to multicollinearity.

Table 8. Associations of cART-regimens (only those significantly associated with multiple symptoms) with past-week non-adherence among ART-initiated adolescents, all potential covariates simultaneously added to the model (*N*=468)

	Outcome: past-week non-adherence	
Exposure variables	**aOR (95% CI)**	***p*-value**
TDF + FTC + EFV (FDC) regimens (Y/N)	0.44 (0.21 - 0.93)	0.032*
D4T-containing regimens (Y/N)	0.67 (0.28 - 1.63)	0.380
LPV/r-containing regimens (Y/N)	0.80 (0.42 - 1.50)	0.477
Clinic staff problems (Y/N)	1.72 (1.11 - 2.67)	0.015*
Clinic transport problems (Y/N)	1.47 (0.94 - 2.30)	0.090*
Clinic facility problems (Y/N)	1.13 (0.70 - 1.82)	0.612
≥3 medication symptoms (Y/N)	1.15 (0.70 - 1.89)	0.572
Positive status knowledge (Y/N)	1.30 (0.70 - 2.41)	0.399
Age	1.02 (0.90 - 1.16)	0.736
Female gender (Y/N)	0.90 (0.58 - 1.41)	0.648
Rural residence (Y/N)	1.12 (0.66 - 1.90)	0.682
Past-month poor health (Y/N)	0.77 (0.49 - 1.23)	0.271
Food insecurity (Y/N)	2.02 (1.09 - 3.76)	0.027*
Lack access to basic necessities (Y/N)	0.86 (0.53 - 1.40)	0.549
Orphanhood (any)	0.85 (0.54 - 1.35)	0.501
Antibiotics/TB treatment (Y/N)	0.90 (0.48 - 1.67)	0.729
≥5 pills/day (Y/N)	0.71 (0.44 - 1.17)	0.181
Daily dosing frequency ≥2 (Y/N)	1.46 (0.87 - 2.44)	0.153
Past-year ARV stock-outs (Y/N)	2.55 (1.02 - 6.39)	0.045*
Recent CD4+ <500 cells/μL (Y/N)	1.44 (0.72 - 2.88)	0.309
Recent treatment failure/VL >1 000 copies/mL (Y/N)	1.86 (0.79 - 4.38)	0.154
Any opportunistic infections (Y/N)	1.54 (0.94 - 2.50)	0.086*
Vertical infection (Y/N)	0.58 (0.27 - 1.26)	0.169
Time on treatment	1.02 (0.96 - 1.08)	0.604

cART = combination antiretroviral therapy; ART = antiretroviral therapy; TDF = tenofovir; FTC = emtricitabine; EFV = efavirenz; FDC = fixed-dose combination; d4T = stavudine; LPV/r = ritonavir-boosted lopinavir; aOR= adjusted odds ratio; CI = confidence interval; Y = yes; N = no; TB = tuberculosis; ARV = antiretroviral; VL = viral load.
*Effects significant at $p<0.1$.

13%; $p<0.001$), but they were not significantly different with regard to any other factors tested (Table 1). Of the included HIV-positive adolescents (*n*=501), median age 14 years (IQR 12 - 16), 97.4% were Xhosa speaking, 80.4% were urban dwellers, 82.4% lived in formal housing, 54.3% were girls, 66.5% were vertically infected, 85.2% knew their own HIV status, and 67.5% lacked access to basic necessities (Table 2).

Prevalence of cART regimens, multiple symptoms and non-adherence

The most common cART regimens were ABC + 3TC + EFV (*n*=165, 32.9%) and TDF + FTC + EFV (*n*=116, 23.2%) (Table 2). For NRTI-based regimens, the prevalence was 46.1% for ABC-containing, 28.5% for TDF-containing and 10.2% for AZT-containing regimens, 7.6% for 3TC-monotherapy, and 6.4% for d4T-containing regimens. For NNRTI-based regimens, the prevalence was 70.7% for EFV-containing and 0.6% for NVP-containing regimens. For PI-based regimens, the prevalence was 17.0% for LPV/r-containing regimens. Reported symptoms were skin rash (44.5%), diarrhoea (43.7%), nausea/vomiting (43.3%), tiredness (42.1%), stomach problems (40.3%), dizziness (33.3%), ear problems (31.9%), sleep problems/bad dreams (29.7%), weight loss (26.2%) and anxiety (2.4%). The overall prevalence of multiple (>3) symptoms was 59.7% (95% CI 55.3 - 63.9) and the prevalence of past-week non-adherence was 29.7% (95% CI 25.9 - 33.9).

Associations of cART regimens with reports of multiple symptoms among adolescents

Independent of covariates, d4T-containing regimens were significantly associated with higher odds of reporting multiple symptoms (adjusted odds ratio (aOR) 3.38; 95% CI 1.19 - 9.60) compared with other NRTI-based regimens (Table 3). Treatment with the FDC containing TDF + FTC + EFV was independently associated with higher odds of reporting multiple symptoms (aOR 2.67; 95% CI 1.21 - 5.88) compared with all other EFV-containing regimens combined (Table 4). LPV/r-containing regimens were significantly associated with lower odds of reporting multiple symptoms compared with EFV-containing regimens (aOR 0.47; 95% CI 0.21 - 1.04) (Table 5). Considering only EFV-containing regimens, adolescents on d4T + 3TC + EFV and TDF + FTC + EFV were more likely to report multiple symptoms than those on ABC + 3TC + EFV (aOR 3.26; 95% CI 1.01 - 10.52, aOR 2.86; 95% CI 1.35 - 6.05 and aOR 1.08; 95% CI 0.64 - 1.82, respectively) (Table 6). When all covariates were held at their mean values in marginal-effects models, the predicted probability of reporting multiple symptoms was 40.0% for HIV-positive adolescents who did not report any of these regimens. For the average adolescent on LPV/r-containing regimens, the predicted probability of reporting multiple symptoms was 49.0%. With the FDC containing TDF + FTC + EFV, the predicted probability of reporting multiple symptoms was 76.0%. With d4T-containing regimens, the predicted probability of reporting multiple symptoms was 80.0% (Fig. 1).

Associations of cART regimens with reports of past-week non-adherence among adolescents

Among regimens that were significantly associated with multiple symptoms, only the FDC of TDF + FTC + EFV was associated with reduced non-adherence (i.e. higher adherence) among adolescents, independent of covariates (aOR 0.44; 95% CI 0.21 - 0.93) (Table 8). Multiple symptoms were not significantly associated with non-

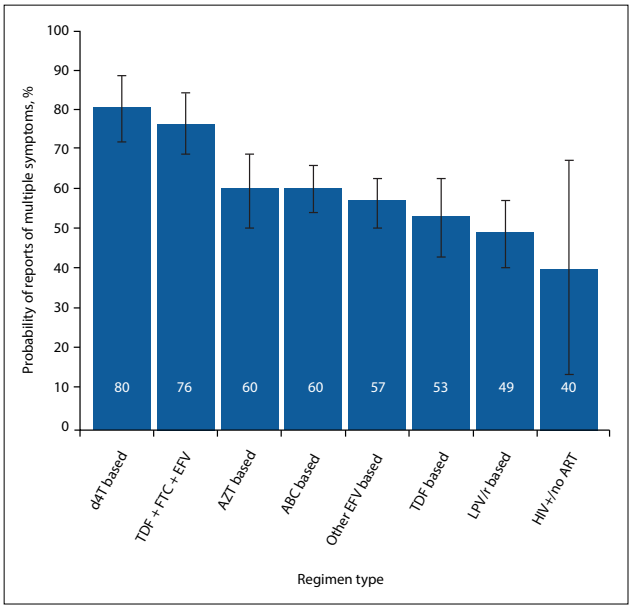

Fig. 1. Marginal-effects model predicting the probability of multiple symptoms among HIV-positive adolescents, according to combination antiretroviral therapy status. (d4T = stavudine; TDF = tenofovir; FTC = emtricitabine; EFV = efavirenz; AZT = zidovudine; ABC = abacavir; LPV/r = lopinavir/ritonavir; HIV+ = HIV-positive; ART = antiretroviral therapy.)

adherence in this model (aOR 1.15; 95% CI 0.70 - 1.89). No other ART regimens were shown to be significantly associated with non-adherence in models testing the relationship between all major cART and past-week non-adherence in this study (results available on request).

Discussion

This study is the first to test associations between cART regimens and reports of multiple symptoms among HIV-positive adolescents, using a large community-traced sample from SA. These findings have several implications for ART programming in sub-Saharan Africa. First, HIV-positive ART-experienced adolescents have a large burden of multiple symptoms. Nearly two-thirds of the adolescents in our study had experienced three or more symptoms in the past 6 months. Reports of multiple symptoms were most common in adolescents on d4T-based regimens and the FDC containing TDF + FTC + EFV. Second, adolescents on LPV/r were protected against most mild to moderate symptoms, notably against dizziness (Table 7). These results are similar to those of studies in high-income settings.[22,23] In this study, the predicted probability of reporting multiple symptoms doubled for adolescents on d4T-containing regimens and those on the FDC containing TDF + FTC + EFV, and increased by only 9% for adolescents on LPV/r-containing regimens compared with those who did not report being on any of these regimens. Third, despite the unfavourable symptom profile, adolescents on TDF + FTC + EFV were the most adherent sub-group by self-report, suggesting that multiple symptoms did not have a major influence on non-adherence when pill burden and daily dosing frequency were substantially reduced. Alternatively, this better adherence may explain why adolescents on TDF + FTC + EFV reported many symptoms.

In clinical practice, it is often suggested that the observed association between TDF + FTC + EFV and self-reported side-effects is mainly due to its EFV component and that the side-effects profile of TDF + FTC + EFV may not be different from that of other EFV-containing regimens, despite its being an FDC. Our findings show that adolescents on TDF + FTC + EFV had about 2.5 times higher odds of reporting multiple symptoms compared with those on other EFV-based regimens. Among EFV-based regimens, adolescents on d4T + 3TC + EFV had higher odds of reporting multiple symptoms compared with those on TDF + FTC + EFV and ABC + 3TC + EFV (in that order of decreasing odds), suggesting that the NRTI backbone may play a more important role in cART symptoms profiling than the NNRTI component.

Our findings show that adolescents on LPV/r-containing regimens reported the least number of symptoms. However, looking at the three common LPV/r-containing cART regimens in this study (Table 7), the number of symptoms reported by adolescents on AZT + 3TC + LPV/r and ABC + AZT + LPV/r was higher than that reported by those on ABC + 3TC + LPV/r and comparable to that reported by those on d4T + 3TC + EFV. This suggests that when AZT is present in an LPV/r-containing regimen, the symptoms profile is comparable to that of d4T-based regimens. Our data cannot explain the cause of this variation, and we recommend further examination.

Study limitations

This study has notable limitations. First, more than half of the interviewed sample (53.0%) was excluded owing to unclear or missing information in patient files and participant responses. Our findings may therefore have suffered from selection bias. Compared with those included, excluded adolescents were significantly younger, and more likely to be food insecure and non-adherent to medication. Of the excluded sample (n=558), 50.4% did not know their medication and what it was for. It is likely that these were adolescents whose status had not yet been disclosed to them. It is possible that the most vulnerable adolescents were excluded from analysis. Recent studies have shown an association between HIV status disclosure and increased adherence to ART among adolescents.[5] By excluding these adolescents, we have under-reported non-adherence rates in this study and this may have attenuated the relationship between cART regimens and past-week non-adherence. However, to report symptoms associated with ART use, participants had to be on ARVs at the time of the study. It is therefore unlikely that these exclusions affected the main objective of the study, which was to examine the relationship between cART regimens and multiple symptoms. Instead, including these adolescents would have confounded this relationship, since some of them were defaulters and symptoms reported by defaulters were likely to be due to virological activity rather than the ARV regimens they were taking. Moreover, analyses were based on a sufficiently large sample to enable detection of a true effect if one existed (n=501, 47.0% of those included), compared with existing studies of ART outcomes in children.[8,17,21]

Second, as this was a community study, we did not conduct clinical assessments for ART-related lipodystrophy/lipoatrophy and dyslipidaemia commonly associated with d4T and LPV/r treatment. We also did not objectively measure AZT-associated anaemia and neutropenia or conduct other biochemical/haematological assessments. In addition, we excluded reports of headaches (a common side-effect associated with AZT use[48]) from analysis because of similar rates among HIV-positive participants and community controls. It is therefore possible that we have underestimated the extent of symptoms associated with cART use in our sample.

Third, our data are cross-sectional and we therefore cannot conclude causality from the observed associations, i.e. we cannot be certain that the symptoms analysed were indeed caused by the medication. Nevertheless, we included a wide range of *a priori* covariates in all logistic regression models to minimise the effects of confounding in non-randomised designs. However, this strategy

could have led to low power and over-adjusted odds ratios. In addition, we cannot rule out that regimens with high rates of multiple symptoms had these because they also had the highest rates of adherence. Similarly, regimens with low adherence may have had lower rates of side-effects in the analysis, even though these could be the drugs that actually cause the most side-effects when taken as prescribed.

Fourth, most outcomes were measured by self-report on past events, so recall and social desirability bias could have played a role in our findings. Moreover, in an attempt to keep the questionnaire brief, some symptoms that are clinically distinct were combined, e.g. shingles and skin rash. However, our assumption was that HIV-positive adolescents in this very resource-limited setting were more likely to be knowledgeable about skin rash than shingles (varicella zoster), therefore making our findings less likely to be confounded by the opportunistic infection.

Fifth, we analysed multiple symptoms (a summation of 10 mild to moderate symptoms) as a dichotomous variable to generate two groups that could benefit from targeted clinical intervention. For instance, those who report less than three symptoms could benefit from symptoms counselling, while those who report three or more symptoms could be offered counselling and/or regimen modification if warranted. However, there is a debate in the literature about the statistical effects of categorisation of continuous variables[49-51] and methods used in cut-off determination.[52-56]

Sixth, adolescents who only reported broadly that they were on an FDC (n=11) were not included in the analysis, because this term is neither specific nor unique to ART. For instance, FDC can be used in reference to TB medication or various duo/triple ART co-formulations such as rifampicin + isoniazid (TB medication), or ABC + 3TC and AZT + 3TC (dual ART combination pills). However, according to the 2015 South African national ART guidelines,[6] this term was often used in reference to TDF + FTC + EFV, and the prevalence of TDF + FTC + EFV use in the full sample is therefore likely to be larger than reported.

Despite these many limitations, this study is unique in that it is the first to use a large community-traced sample of HIV-positive adolescents enrolled on national ART programmes, thus providing preliminary evidence from real-world resource-constrained settings. Findings from a community-based sample have better external validity than those from a clinic-based sample. While these findings should be tested in other settings within and outside SA to check reproducibility, with randomised and longitudinal study designs to test causality, the study population and setting are reasonably representative of other low-resource settings in sub-Saharan Africa.

Conclusions

In our sample of 10 - 19-year-old HIV-positive ART-experienced SA adolescents, rates of multiple symptoms were high. Our findings support the WHO-recommended discontinuation of d4T use. ART provision should be accompanied by counselling on symptoms as part of routine HIV management. Simplified regimens have the potential to increase adherence among adolescents, so more one-pill-a-day FDC ARVs are urgently needed. Our findings underscore the dilemma faced by clinicians when choosing between low-toxicity regimens and those that promote ART adherence, and can contribute to informing age- and context-appropriate treatment guidelines. It is important for these findings to be tested in future longitudinal or randomised designs that measure clinical staging, VL, CD4+ count and health symptoms prior to cART initiation and outcome assessment.

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Conflicts of interest. None.

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