Differing psychological vulnerabilities among behaviourally and perinatally HIV infected adolescents in South Africa – Implications for targeted health service provision.

Authors L. Sherr[1], L. Cluver[2,3], E. Toska[4,2] E He[5]
[1]UCL, London, United Kingdom, [2]University of Oxford, Dept of Social Policy and Intervention, Oxford, United Kingdom, [3]University of Cape Town, Dept of Psychiatry and Mental Health, Cape Town, South Africa, [4]University of Cape Town, AIDS and Society Research Unit, Cape Town, South Africa, [5]Washington University in St. Louis, St Louis, MO, USA

Contact Prof Lorraine Sherr l.sherr@ucl.ac.uk

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Abstract

HIV infections are growing the fastest amongst adolescents, especially in sub Saharan Africa. On reaching adolescence, perinatally-infected youth may have different needs to those who acquired infection behaviourally. Yet both have sub-optimal adherence with implications for their own health as well as onward transmission. This study uses the world's largest community-based study of HIV-positive adolescents from the Eastern Cape, South Africa. Clinic records at N=53 district health facilities generated a log of all ART-initiated adolescents who were then interviewed in the community: N=1058 (90%) were tracked and participated. Ethical approval, informed consent and data collector training preceded data gathering. Inventories comprised validated measures of mental health (depression, anxiety, suicidality and internalised stigma), substance use, ART adherence, and clinic attendance. Analyses were conducted using SPSS25 and STATA15. Perinatally-infected adolescents (n=792, 77.3%) were significantly more likely to be ART adherent (OR=1.54 95%CI: 1.14-2.07 p=0.005), retained in healthcare (OR=1.59 95%CI1.18-2.14 p=0.002), and treated well by clinic staff (OR=2.12 95%CI1.59-3.07 p≤0.001). Behaviourally-infected adolescents were more likely to be depressed (B=0.81 p≤0.001), anxious (B=1.36 p≤0.001), report internalised stigma (B=0.91 p≤0.001), express suicidal ideation (OR=3.65 95%CI: 1.96-6.82 p≤0.001) and report excessive substance use in the past year (OR=9.37 95%CI5.73-15.35 p≤0.001). Being older explained most of these differences, with female adolescents living with HIV more likely to report suicidal ideation. However, behaviourally-infected adolescents were more likely to report substance use (OR=2.69 95%CI: 1.48-4.91 p=0.001), depression (B=0.406, p=0.022), anxiety (B=1.359, p≤0.001), and internalised stigma (B=0.403, p=0.007) in multivariate regression analyses, controlling for covariates. Moderation analyses (adjusting for multiple testing) suggest that behaviourally-infected HIV-positive adolescents who are also maternal orphans are more likely to report higher rates of depression (B=1.075, p<0.001). These notable differences by mode of infection suggest that studies which conflate HIV-positive adolescents may blur the clinical and psychological experiences of these two different sub-populations. Drivers of non-adherence, poor retention in care, and mental health problems may differ by mode of infection, requiring tailored interventions. Health and social service provision, if it is to be effective, needs to address these different youth profiles to ensure optimal adherence, development and wellbeing throughout the life course.

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Background

HIV is the leading cause of adolescent death in sub Saharan Africa (Slogrove et al 2017). Although great strides have been made in terms of treatment efficacy, ART rollout, mortality and strategic plans to eliminate parent-to-child transmission in the adult population (Reniers et al 2014), the epidemic amongst adolescents is not under control. Karim et al (2017) showed dramatic increases in adolescent HIV incidence when comparing adolescents to cohorts of other ages, with marked increases in young women (Delva et al 2014). A global initiative to target prevention in adolescents – the DREAMS project – aims to tackle HIV in this group, while national programmes such as Option B+ for pregnant mothers aim to eliminate paediatric HIV and therefore minimise the numbers of adolescents living with HIV from birth.

However, the evidence base on adolescent HIV needs to provide more rigorous insight into HIV management. Despite calls for differentiated care as an approach to deliver tailored appropriate services, research on HIV-positive adolescents suggests several emerging issues and gaps. Treatment rollout is lowest among this age group (Zanoni et al. 2016), in part due to lower access to HIV testing (Shisana et al. 2014). Adherence to treatment when it is available is not optimum, with adolescents reporting higher rates of non-adherence and treatment interruption than children and adults (Kim et al 2017, Cluver et al 2016, Evans et al 2013). Structural drivers of non-adherence and risk behaviours need to be explored, with poverty, hunger, violence victimisation and mental health being powerful drivers of risk behaviours, including treatment non-adherence (Cluver et al. 2018).

Adolescents living with HIV comprise two different sub-populations: those who are infected through sexual exposure (behaviourally or horizontally infected) and those infected through parent-to-child transmission (perinatally or vertically infected), now surviving into adolescence. It is estimated that about one third of HIV-infected infants can survive into adolescence even if untreated (Ferrand et al. 2009) – but with numerous health challenges such as cardiac disease (Miller et al 2013). The passage of time shows the growth of this cohort with much focus on transition to adult care, but less on the groups of adolescents themselves. A recent review of the 15 highest burden adolescent HIV countries reported that there were "no systems tracking adolescent transition to adulthood or healthcare transition" (Miller et al 2013). These authors called for disaggregation of data, particularly exploring mode of infection where possible so that the needs of adolescents could be better catered for. A systematic review of adolescent needs found few studies in sub Saharan Africa where the greatest numbers live (Dahourou et al 2016). These authors suggested a need to focus on sub groups so that treatment and resources could be adequately targeted. Bailey et al (2017) differentiate between the

needs of perinatally-infected groups and sexually- or intravenously-infected groups in the Caribbean, Central and South America, Eastern Europe and Asia and Pacific regions. They note the former are often facing the effects of parental death, lost family support, stigma, parental drug use, late status disclosure and socioeconomic challenges. The latter were often members of marginalized groups with difficulties accessing HIV treatment services. However, no data was provided for Sub Saharan Africa where the issues may well be similar or substantially different. The review of adolescents in key populations yielded similar findings (Lall et al 2015) with a call for services to be tailored to unique needs of sub-populations.

In addition to treatment and care, a recent systematic review finds that sexual risk behaviours amongst adolescents living with HIV is another key area of need as they may pose a number of threats in terms of wellbeing, relationship formation, onward transmission of HIV, unwanted pregnancies and other sexually transmitted diseases (Toska et al 2017). This review logged high sexual risk behaviour across 35 studies, but with unclear determinants and few studies examining interventions. No differentiation between perinatally- or behaviourally-infected adolescents was found in the included studies.

The general HIV prevention and treatment literature has shown that broad-brush approaches may miss key populations, specific groups or hard-to-reach populations. Within adolescents it is unclear how interventions should be adjusted to accommodate such subgroups. The literature does describe some major challenges for adolescents, (Govindasamy et al 2014) especially in terms of successful engagement and retention in care, with fewer studies on adolescents than adults (Murray et al 2017). The major focus of subgroups has been aimed at gender differences. This has been a key lens as there are specific gender related differences in adolescents as well as variation of interventions' efficacies by gender. Another lens may relate to mode of infection but very few studies explore this concept. In resource-poor settings, with fractured medical care and interrupted provisions, many adolescents who appear in clinics may be grouped together by age and gender rather than a clear understanding of their particular needs. There are clear barriers in policy implementation for this group and a general call to understand subgroups, drivers and promising practices if services of quality are to evolve (Mark et al 2017).

To guide interventions and planning, it is important to discern health factors associated with perinatally- and behaviourally-acquired HIV in adolescents in Southern Africa. We hypothesise that mode of infection is associated with different drivers and experiences, with implications for care, support and management.

Methods

The study reports on data from the Mzantsi Wakho baseline of HIV-positive adolescents residing in the Eastern Cape, South Africa (Cluver et al 2016). Every adolescent who ever initiated ART in an urban/rural health district was eligible for inclusion in the study. All 53 public health facilities providing ART were visited, and all adolescents with paper or computerised records aged between 10-19 were identified and followed up at clinics or home to ensure inclusion despite clinic attendance rates. This resulted in a 90.1 % interview response rate of those eligible for inclusion. Refusal rates were 4% with the remainder being untraceable or experiencing cognitive delay too severe for informed consent. This generated a sample of 1,058 adolescents who were interviewed with standardised questionnaires and provided consent (adolescents and their primary caregivers) to access full clinic notes. Included adolescents did not differ from those not included on variables of age, gender or urban/rural residence.

Trained data collectors administered detailed individual interviews collecting data on demographic information, parental death, health, risk, psychosocial factors, treatment access and adherence using validated scales, where available. Interviews were researcher administered with full consent from caregivers and adolescents, lasting around 90 minutes using tablets and versions in the language of their choice (Xhosa or English). Questionnaires were translated and back translated for accuracy. Ethical approval was granted by the University of Cape Town (CSSR 2013/14), Oxford University (SSD/CUREC2/12-21) as well as provincial and hospital review committees.

Measures

Depression was measured using the Child Depression Inventory short form (Cronbach α=.64 reliability) (Kovacs, 1992). **Anxiety** was measured using the Children's Manifest Anxiety Scale short 14-item form, α=0.80 (Reynolds and Richmond 1978, Boyes et al 2013). **Posttraumatic stress symptoms** (Amaya-Jackson et al 1995) included a 19-item form α=.89. **Suicidality/self-harm** was measured using the Mini International Neuropsychiatric Interview (Sheehan et al 2004) 5 items, α = .87. **Internalised stigma** was measured using an adapted form from Wright et al 2007 – ALHIV-SS, α=.75 for internalized stigma (Pantelic 2016). **ART adherence** involved self-report (Evans et al 2015) with an adapted version of the Patient Medication Adherence Questionnaire (Duong et al 2001). **Retention in care** was measured as attending all clinic appointments in the past year and full past-week adherence to antiretroviral therapy, following WHO recommendations (Rollins et al 2014).

Mode of infection (MOI) was measured using an age cutoff, validated with a detailed algorithm in the absence of definitive clinic notes ascribing mode of infection. Participants' MOI were initially assigned with the cutoff age of 10, based on existing Sub-Saharan African paediatric HIV cohorts (CIPHER Global Cohort Collaboration 2018). Those who began ARVs before the age of 10 were designated as perinatally-infected and those who began ARVs at 10 years old and after were designated as behaviourally-infected. An algorithm evaluated the consistency of the initial designations with

inconsistent designations being recoded when strong evidence was available. Amongst those initially designated as behaviourally-infected, early sexual activity, risky behaviour and absence of an HIV-infected parent served as evidence for behavioural infection. Amongst those initially designated as perinatally-infected, HIV-infected parents, parental orphanhood, no sexual activity, history of chronic illness and early ARV initiation year supported vertical infection. Re-determination of MOI happened in both directions: amongst adolescents initially designated as behaviourally-infected, lack of sexual history and having parents infected with HIV resulted in recoding into perinatal infection. For those initially designated as perinatally-infected, neither parents having a history of HIV, no history of chronic illness or cognitive issues resulted in recoding into behavioural infection.

Analyses

A total of N=1,024 HIV-positive adolescents were included in the analyses. Thirty-four HIV-positive adolescents were not included due to inability to definitively determine their MOI. Socio-demographic descriptive statistics were performed on the entire sample and the MOI sub-samples. Analyses was conducted in five stages. First, bivariate statistics were performed to compare socio-demographic characteristics, clinic and psychological outcomes between perinatally- and behaviourally-infected adolescents living with HIV. Second, logistic and linear regression analyses were used to assess to the effect of MOI on these outcomes, controlling for all covariates which differed significantly by mode of adolescent HIV infection. Third, interaction effects of mode of infection with socio-demographic factors significantly associated with each outcome were selected for multiple testing using the Benjamini Hochberg's step-down adjustment approach (Benjamini & Hochberg 1995). Fourth, a final model including mode of infection as the outcome variable and all health outcomes investigated the burden of combined health factors for the two modes of infection. Finally, marginal effects modelled the probability of combinations of significant outcomes by mode of infection.

Results

Initial MOI coding designated n=650 as perinatally-infected and n=375 as behaviourally-infected. After the MOI validation, n=792 were confirmed as perinatally-infected and n=232 as behaviourally-infected; five participants were removed due to lack of data to validate MOI (Figure 1).

Insert figure 1 here

Adolescents who were behaviourally infected were more likely to be female, older, paternal orphans, and lack basic necessities at home. A higher proportion of perinatally-infected adolescents were maternally orphaned (Table 1). The two groups of adolescents did not differ by type of residence (rural vs urban), housing (informal vs. formal) and levels of double orphanhood.

Insert table 1 here

Compared to their perinatally-infected peers, behaviourally-infected adolescents reported higher rates of poor clinic experience, worse retention in care, and be ART non-adherent (p≤0.005). They also reported to feel greater levels of internalized stigma, anxiety, depression, suicidality, and engage in excessive use of drugs and alcohol (p≤0.001) (Table 2).

Insert table 2 here

However, after controlling for significant covariates, only depression, anxiety, internalized stigma, and substance use remained significantly associated with being behaviourally-infected (Table 3).

Insert table 3 here

In multivariate models (Table 3), behaviourally-infected adolescents were more likely to report higher levels of depression (B=0.456, p=0.018), anxiety (B=1.192 p<0.001), internalized stigma (B=0.41, p=0.008), and substance use (OR=2.99 p=0.001). Older adolescents were more likely to be treated less kindly at the clinic OR=0.88 p<0.001), drop out of care (OR=0.92 p=0.004), report depression (B=0.09 p<0.001), internalized stigma (B=0.13 p<0.001), suicidality (OR=1.22 p=0.01), and substance use (OR=1.43 p<0.001). HIV-positive adolescent girls were more likely to report suicidal ideation OR=2.43 p=0.025).

Moderation analyses tested whether depression, anxiety, internalised stigma and substance use differed by mode of HIV infection and socio-demographic variables. Four interaction terms were tested for each significant outcome (mode of infection*age, mode of infection*gender, mode of infection*poverty, mode of infection*maternal orphanhood, mode of infection*paternal orphanhood). After adjusting for multiple testing, mode of infection moderated the effect of maternal orphanhood on depression: HIV-positive behaviourally infected adolescents who were maternal orphans were more likely to report depression (Figure 2).

Insert Figure 2 here

Figure 3 address the syndemic nature of psychological issues and sets out the number of psychological morbidities above the cut off scores experienced by adolescents from the two mode of infection groups.

Insert Figure 3 here

A multivariate model of all factors and mode of infection suggests that controlling for socio-demographic factors and other physical, clinic-related and mental health experiences, behaviourally-infected adolescents are more likely to report higher rates of anxiety (OR1.13 p=0.016), internalised stigma (OR=2.85 p=0.0010), and excessive substance use (OR=2.33 p=0.011). The probability of being

behaviourally infected increased with each additional mental health issue experienced by the participants, with the highest among participants who reported all three (Figure 4).

Insert Figure 4 here

Discussion

The results presented show many of the challenges faced by adolescents living with HIV, including a high level of orphanhood and parental death. There is a global call to focus on the particular needs of adolescents (Pettifor et al 2018, Bekker 2015) and this data highlights such needs. The group in this study logged multiple deprivations which needs to be considered in programming, with 68% lacking in the very basic of necessities. This was true of all adolescents, independent of mode of infection, although behaviourally-infected adolescents lived in poorer households confirming linkages between structural deprivation and HIV infection (Cluver et al. 2011, Seeley et al 2012). Moderation effects suggesting that behaviourally infected adolescents were more likely to experience depression if they were maternal orphans also highlight the potential pathway between mental health and HIV infection (Cluver et al 2016, Operario et al 2007).

This large study revealed that in a community-traced population of HIV-positive adolescents, the ratio of behavioural to perinatal infection was 1:3. Mode of infection was a factor in differentiating groups of adolescents in terms of clinic-related and mental health outcomes. A recent review (Lam, Fidler and Foster 2017) examining the transition experiences of these two groups of adolescents found variation and similarities in their experiences, but noted that data from Africa was sparse. These data may supplement the global understanding for these groups. In this study, those who were behaviourally-infected were significantly less likely to have a good experience while receiving care in the clinic. Those infected from birth may have had more experience of clinic attendance and more familiarity with staff. Harsh attitudes towards adolescents who acquire HIV through sexual transmission may be counterproductive in helping them engage in care. Additionally, behaviourally-infected adolescents reported worse rates of adherence to ART and retention in care. This has been also documented in studies in other settings such as the USA (MacDonell et al 2013), which suggest that perinatally-infected adolescents had more treatment experience. Such outcomes, clustered in a scenario of disengagement, may perpetuate poor treatment involvement to the detriment of both the adolescent themselves and to sexual partners if they are not virally suppressed. Behaviourally-infected adolescents reported significantly higher internalised stigma, which may be another barrier to treatment engagement, disclosure and self-care. This group also reported significantly worse levels of anxiety, higher depression scores and higher reported substance use, and were more likely to report two or more mental health issues concurrently – suggesting a syndemic of mental health challenges for behaviourally-infected adolescents. The cross-sectional data cannot determine cause and effect, and it may well be that mental health problems were a factor in HIV exposure in the first place, as well as potentially a consequence of HIV infection. However, it is clear from this data that these adolescents could certainly benefit from mental health interventions and support – especially given the elevated suicidal tendencies that were also recorded. Such integrated provision needs have been highlighted in reviews with data mostly from high resource settings (Lam et al), and this data from a lower resource setting endorses these findings.

The multivariate analysis shows that the contribution of both age and gender is a factor to be considered, with female participants being more likely to experience elevated mental health scores, especially suicidal ideation – in line with global burden of disease statistics.

The differences in these groups may have numerous explanations. Firstly, those who are infected perinatally will have a parent also infected and, if that parent is surviving, could benefit from such shared experience as well as long term linking into clinics and HIV management systems. However, they may also have extended exposure to treatment and HIV clinic care, more time for adherence and drug resistance issues to challenge their care regimens, and more opportunity for stigma and other challenges to be faced (Lowenthal 2014). Sibling infection may also be a factor in treatment adjustment. Behaviourally-infected adolescents may not have such social support, suffer from internalised stigma, and may be particularly vulnerable to discrimination at home and at health facilities. This group may also have pre-existing challenges which placed them at risk of infection in the first place. Two findings are of additional note. Maternal orphaning was a significant factor and the long term ramifications of maternal death and the absence of a mother during childhood needs to be monitored. Also the literature on syndemics resonates in this data, where multiple forms of psychological challenge are encountered by many.

The study has some limitations which need to be taken into consideration. In geographical areas where there are good medical records, perinatally- and behaviourally-infected groups can be more easily confirmed and the limitations of large cohorts with no historical data is one we faced, compounded by incomplete notes. By using clinic engagement as an entry point, our data may miss behaviourally-infected adolescents who have not yet tested, which is common within this age group. However, our results are likely to be conservative estimates as those not yet engaged in care are likely to have worse clinical outcomes. Furthermore, although the sample is robust, the data are cross sectional and longitudinal data would be needed to determine causality to document change over time and how the effect of mental health factors may shape clinical outcomes for different sub-groups by mode of infection. Additionally, there were limitations in methodology as the Cronbach's alpha for depression was low, indicating less than ideal internal consistency for the depression measure.

This study also has its advantages. Because the participants were traced back to their communities for interviews, the results have high external validity when comparing amongst other South African and sub-Saharan communities' HIV-positive adolescent populations who had ever initiated on ARVs. This is also reinforced by the fact that there was no difference in age, gender and urbanicity for those who were surveyed and those who were not. Where possible, validated mental health and clinic-related outcomes measures were used (Boyes 2013, Cluver 2015, Pantelic 2016). The data is from the baseline study of a longitudinal cohort so these exploratory results can inform longitudinal analyses. Particularly, important future questions include the potential for mode of infection to interact with other known risks for health and mental health outcomes, for example poverty, abuse and orphanhood.

The data clearly suggests that a tailored approach to adolescent groups is needed to maximise linkage to care and appropriate provision. Support and improved service provision is needed on three levels – individual, community and clinic. At the individual level, the groups differ in terms of their history, their exposure to HIV and their sexual behaviour. While an adolescent who is exposed behaviourally may have several sexual risks, a perinatally-infected adolescent may be HIV-positive in the absence of any sexual behaviour. Interventions based on assumptions of sexual behaviour may misfire. Community needs relate to support and stigma amelioration. It may be that perinatally-infected adolescents live in an environment where HIV has been present for longer than behaviourally-infected adolescents. Their age, length of time living with the virus, and having family members undergoing similar care needs may be a factor in coping and adjustment. From the level of the clinic, it is vital that harsh approaches are curtailed, shouting and reprimanding of adolescents is discouraged, and the opportunity to build good patient-caregiver relationships is encouraged. Clinic staff should be especially vigilant of these guidelines when treating behaviourally-infected adolescents as their shorter history in HIV care in the clinical setting and potentially internalised stigma and guilt from HIV infection may make them more reactionary to negative behaviour by clinic staff. Such provision may immediately curtail a spiral of disengagement, poor appointment keeping and consequent treatment non-adherence. The importance

of good clinical records and accurate information must be stressed so that future management of adolescents will have clear information on mode of infection.

This data shows not only the importance of considering mode of infection when providing for adolescents with HIV, but also the need to understand the milieu in which this group lives – including multiple deprivations, high mental health burden, compound bereavement, challenging engagement with care and services and unacceptable levels of stigma.

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Figure 1. Mode of infection algorithm assignment for HIV-infected adolescents, N=1025
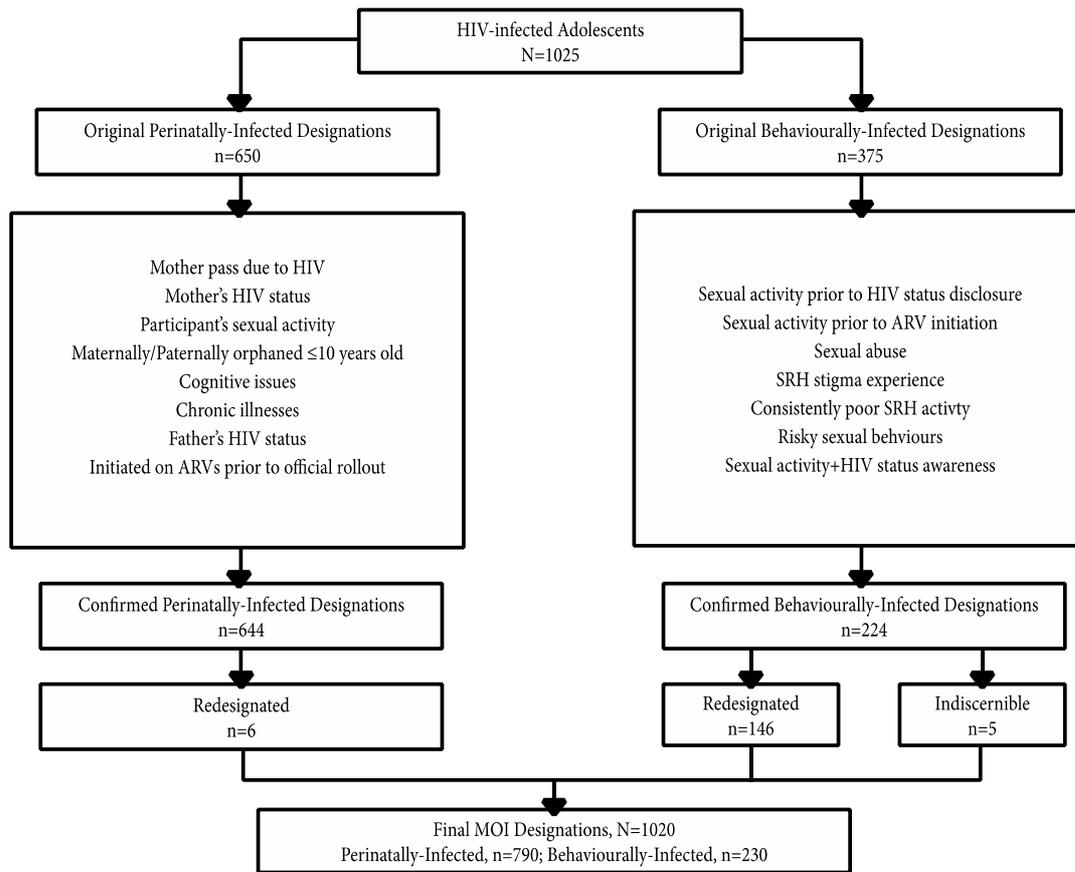
Table 1. Socio-demographics characteristics of HIV-positive adolescents by mode of infection

Characteristics	Total sample (N=1024 N (%) or mean (SD)	Perinatally-infected adolescents (N=792) N (%) or mean (SD)	Behaviourally-infected adolescents (N=232) N (%) or mean (SD)	P-value
Age	13.76 (2.82)	12.87 (2.33)	16.79 (2.16)	≤0.001
Female	553 (54.0)	389 (49.1)	164 (70.7)	≤0.001
Rural residence	229 (22.5)	182 (23.1)	47 (20.3)	0.374
Informal housing	190 (18.6)	139 (17.6)	51 (22.0)	0.129
Poverty [a]	693 (67.7)	519 (65.5)	174 (75.0)	0.007
Maternal orphan	456 (44.5)	377 (47.6)	79 (34.1)	≤0.001
Paternal orphan	311 (30.4)	224 (28.3)	87 (37.5)	0.007
Double orphan	161 (15.7)	119 (15.0)	42 (18.1)	0.257

[a] Missing at least one basic necessity

Table 2. Health/Clinic outcomes by mode of infection

Clinic/ Mental health outcomes	Total sample (N=1024) N (%) or mean (SD)	Perinatally-infected adolescents (N=769) N (%) or mean (SD)	Behaviourally-infected adolescents (N=267) N (%) or mean (SD)	Univariate regression results (reference: perinatally infected) OR (95%CI) P-value
Past-week ART non-adherence	353 (34.5)	255 (32.2)	98 (42.2)	1.54 (1.14-2.08) p≤0.001
Caring staff treatment at clinic	805 (78.6)	649 (81.9)	156 (67.2)	0.45 (0.33-0.63) p≤0.001
Retention in care	615 (60.0)	496 (62.6)	119 (51.3)	0.63 (0.47-0.84) p≤0.001
Depression	1.25 (1.97)	1.07 (1.71)	1.88 (2.58)	B=0.81 p≤0.001
Anxiety	2.16 (2.64)	1.85 (2.40)	3.21 (3.14)	B=1.36 p≤0.001
Internalised Stigma	1.96 (1.67)	1.76 (1.52)	2.67 (1.95)	B=0.91 p≤0.001
Suicidality	42 (4.1)	21 (2.7)	21 (9.1)	3.65 (1.96-6.82) p≤0.001
Substance use	82 (8.0)	26 (3.3)	56 (24.1)	9.37 (5.72-15.35) p≤0.001

Table 3. Comparing perinatally and behaviourally infected adolescents in multivariate regression models

Clinic/ Mental health outcomes	Age (years)	Gender (female)	Poverty	Maternal Orphan	Paternal Orphan	Mode of infection (horizontal)
Past-week ART non-adherence[a]	1.05 (0.99-1.17) 0.092	1.18 (0.91-1.55) 0.216	1.15 (0.87-1.52) 0.332	0.89 (0.68-1.16) 0.384	1.12 (0.83-1.48) 0.484	1.17 (0.80-1.72) 0.420
Caring staff treatment at clinic[a]	**0.88 (0.82-0.95) ≤0.001**	0.85 (0.62-1.17) 0.332	0.94 (0.68-1.33) 0.755	**0.73 (0.53-1.00) 0.049**	1.06 (0.76-1.48) 0.742	0.72 (0.47-1.10) 0.130
Retention in care[a]	**0.92 (0.87-0.97) 0.004**	0.89 (0.68-1.15) 0.356	0.93 (0.70-1.22) 0.566	1.01 (0.77-1.31) 0.971	0.98 (0.74-1.29) 0.860	0.91 (0.62-1.31) 0.605
Depression [b]	**0.09 ≤0.001**	0.04 0.779	0.21 0.115	0.18 0.151	0.03 0.844	**0.46 0.013**
Anxiety [b]	0.04 0.338	0.19 0.246	0.05 0.758	0.19 0.252	0.08 0.657	**1.192 ≤0.001**
Internalised Stigma [b]	**0.13 ≤0.001**	0.03 0.770	0.07 0.510	0.08 0.450	-0.20 0.074	**0.41 0.008**
Suicidality[a]	**1.22 (1.05-1.41) 0.01**	**2.43 (1.12-5.27) 0.025**	1.35 (0.63-2.94) 0.445	1.59 (0.82-3.07) 0.167	1.10 (0.57-2.14) 0.774	1.52 (0.65-3.53) 0.335
Substance use[a]	**1.43 (1.26-1.63) ≤0.001**	0.83 (0.48-1.43) 0.502	1.14 (0.63-2.04) 0.662	1.12 (0.67-1.88) 0.658	1.48 (0.90-2.47) 0.125	**2.99 (1.60-5.61) 0.001**

[a] Results of multivariate logistic regressions models: OR (95%CI), p-value.
[b] Results of multivariate linear regression models B, p-value

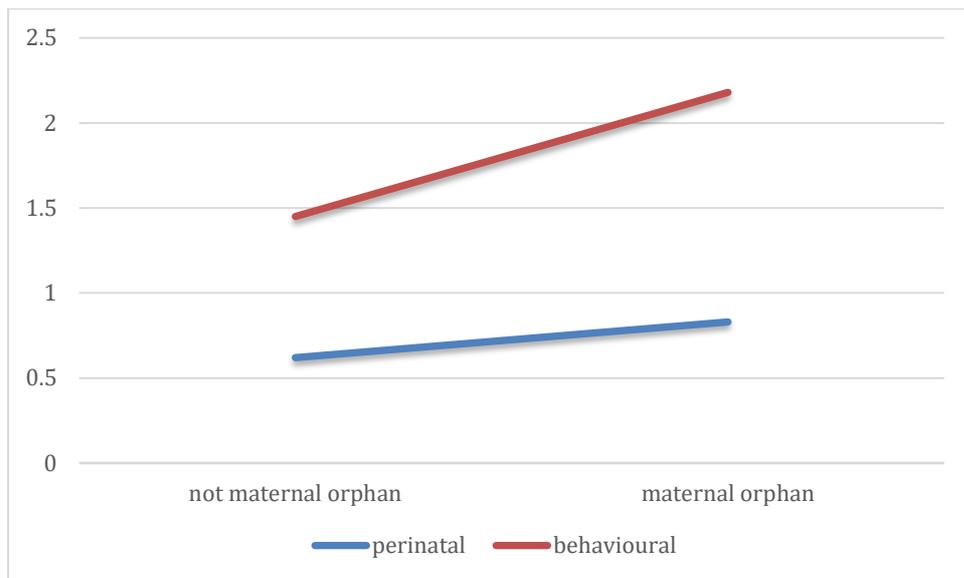*Figure 2. Depression score by mode of infection and maternal orphanhood (unadjusted)*

Table 4. Multivariate regression model of all outcomes and mode of infection (N=1,024)

Factors	Mode of Infection (OR, 95%CI, p-value)
Age	**1.861 (1.698-2.040) ≤0.001**
Sex	1.573 (1.039-2.38) 0.032
Poverty	0.987 (0.639-1.526) 0.954
Maternal orphan	**0.287 (0.188-0.439) ≤0.001**
Paternal orphan	0.783 (0.509-1.204) 0.265
Past-week ART non-adherence	1.449 (0.62-3.388) 0.392
Caring staff treatment at clinic	0.94 (0.582-1.517) 0.800
Retention in care	1.376 (0.593-3.191) 0.457
Depression	1.016 (0.914-1.13) 0.764
Anxiety	**1.103 (1.018-1.194) 0.016**
Internalised Stigma	**2.851 (1.538-5.287) 0.001**
Suicidality	0.884 (0.377-2.077) 0.778
Substance use	**2.328 (1.213-4.467) 0.011**

Figure 4. Psychological Issues by Mode of Infection (% probabilities controlling for covariates)
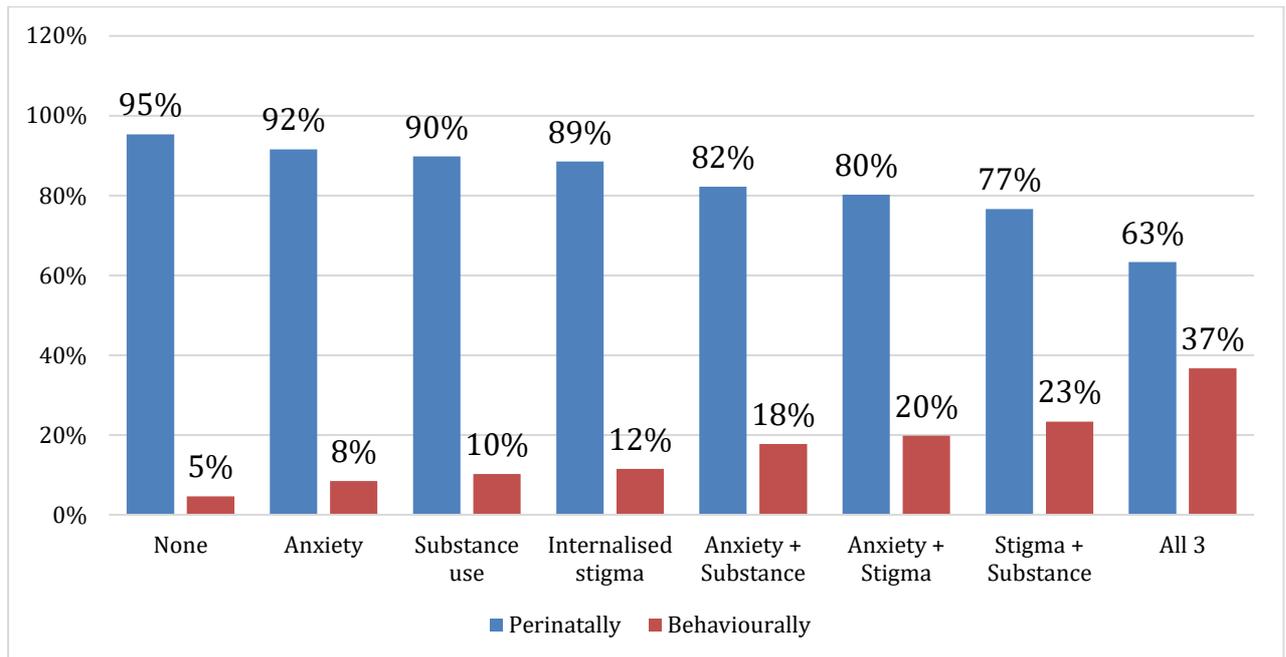
Figure 3. Number of psychological issues by mode of infection