Original research article

INTERNATIONAL JOURNAL OF STD & AIDS

International Journal of STD & AIDS
0(0) 1–11

DOI: 10.1177/0956462417724707
journals.sagepub.com/home/std
SAGE

Significant rates of risky sexual behaviours among HIV-infected patients failing first-line ART: A sub-study of the Europe–Africa Research Network for the Evaluation of Second-line Therapy trial

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Abstract

There are limited data on the prevalence of risky sexual behaviours in individuals failing first-line antiretroviral therapy (ART) and changes in sexual behaviour after switch to second-line ART. We undertook a sexual behaviour sub-study of Ugandan adults enrolled in the Europe–Africa Research Network for the Evaluation of Second-line Therapy trial. A standardized questionnaire was used to collect sexual behaviour data and, in particular, risky sexual behaviours (defined as additional sexual partners to main sexual partner, inconsistent use of condoms, non-disclosure to sexual partners, and exchange of money for sex). Of the 79 participants enrolled in the sub-study, 62% were female, median age (IQR) was 37 (32–42) years, median CD4 cell count (IQR) was 79 (50–153) cells/μl, and median HIV viral load log was 4.9 copies/ml (IQR: 4.5–5.3) at enrolment. The majority were in long-term stable relationships; 69.6% had a main sexual partner and 87.3% of these had been sexually active in the preceding six months. At enrolment, around 20% reported other sexual partners, but this was higher among men than women (36% versus 6.7 %, $p < 0.001$). In 50% there was inconsistent condom use with their main sexual partner and a similar proportion with other sexual partners, both at baseline and follow-up. Forty-three per cent of participants had not disclosed their HIV status to their main sexual partner (73% with other sexual partners) at enrolment, which was similar in men and women. Overall, there was no significant change in these sexual behaviours over the 96 weeks following switch to second-line ART, but rate of non-disclosure of HIV status declined significantly (43.6% versus 19.6%, $p < 0.05$). Among persons failing first-line ART, risky sexual behaviours were prevalent, which has implications for potential onward transmission of drug-resistant virus. There is need to intensify sexual risk reduction counselling and promotion of partner testing and disclosure, especially at diagnosis of treatment failure and following switch to second- or third-line ART.

Keywords

Africa, antiretroviral therapy, high-risk behaviour, HIV, sexual behaviour

Date received: 1 December 2016; accepted: 9 July 2017

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Introduction

There has been remarkable progress in the global scale-up of antiretroviral therapy (ART), particularly in sub-Saharan Africa, where more than 11 million HIV-infected persons have received ART.[1] This has been achievable in part because of adoption of the public health approach with use of simplified standardized treatment regimens and a simplified approach to monitoring.[2] However, it has been increasingly recognized that monitoring ART response based on clinical criteria alone with or without CD4 cell counts rather than viral load measurement detects treatment failure late, and often only after patients have already developed substantial resistance to the antiretroviral drugs.[3] Until recently, there has been limited access to routine viral load monitoring to enable prompt diagnosis of virological failure and switch to second-line ART. At the same time, there continues to be significant rates of ongoing HIV transmission and new infections. In 2015, there were an estimated 2.1 million (1.9 million–2.2 million) new infections in adults, of which 70% occurred in sub-Saharan Africa.[1,4] High rates of late treatment failure and associated drug resistance in the setting of high rates of ongoing HIV transmission in turn raise concerns about the potential for high rates of acquisition of drug-resistant HIV infection. A recent World Health Organization (WHO)[5] global report on drug resistance highlighted significant rates of drug resistance (at or above 15%) among those starting ART in some countries and up to 40% among people restarting treatment. Increasing levels of ART resistance have serious economic implications as second- and third-line ART regimens are three times and 18 times, respectively, more costly than first-line ART.[5]

A key driver in risk of onward transmission of drug resistant virus is the level of high-risk sexual behaviours among those with treatment failure and therefore likely to have drug resistance. Extensive studies on impact of initiation of first-line ART on higher risk behaviours have been inconsistent. In a review of eight cross-sectional and nine cohort studies that assessed the impact of ART on sexual risk behaviours in resource-limited settings, all but one showed beneficial behavioural effects of ART.[6–23] Two further systematic review and/or meta-analyses have also suggested significant reduction in risky sexual behaviour among people on ART in sub-Saharan Africa.[24,25] However, a 2003 study from Côte d'Ivoire reported increased unprotected sex after ART initiation.[10] There have been no published studies on sexual behaviours in persons failing first-line therapy and changes in behaviour after initiation on second-line ART. Such data are important to guide both practical counselling practices and messages for patients starting second-line therapy and to inform parameter inputs on sexual behaviour into ongoing modelling work estimating levels of transmission of drug-resistant virus among those failing ART. We used the opportunity of the Europe–Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial – a large randomized trial of different second-line ART regimens in patients failing first-line ART in sub-Saharan Africa to undertake a sub-study of sexual behaviours in Ugandan participants at two sites and examine the baseline prevalence of risky sexual behaviours and changes over 96 weeks after initiation of second-line ART.

Methods

EARNEST second-line ART trial

We undertook a longitudinal sub-study of the EARNEST Trial – a three arm multi-centre open label randomized controlled trial of HIV-infected persons who had failed first-line nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing ART (ISRCTN-37737787). A total of 1277 participants in 14 centres across five sub-Saharan African countries were randomized between 12 April 2010 and 29 April 2011 to either one of three second-line regimens of boosted Protease Inhibitor (bPI) with either raltegravir, or bPI monotherapy (after a 12-week induction phases with bPI and raltegravir), or standard of care (bPI plus two new NRTIs). Full details of the conduct and results of the EARNEST trial have been published.[26] In brief, eligible patients for the EARNEST trial were adults/adolescents >12 years of age who had taken 2NRTI + NNRTI first-line ART with no interruptions for >12 months, were PI-naive, had missed no more than three days treatment in the preceding month and had immunological or clinical first-line treatment failure defined according to the 2010 WHO criteria and virological failure confirmed by screening HIV viral load (VL) >400 copies/ml. Exclusion criteria were current pregnancy or breast feeding, contraindications, or requirement for concomitant medications interacting with study drugs or were hepatitis B surface antigen positive. Clinic visits were four-weekly to week 24, then six-weekly to week 48, then eight-weekly to week 96, with doctor review at every other visit and ART dispensed at each visit. VL was measured centrally (Joint Clinical Research Center, Kampala, Uganda) on samples stored at weeks 48 and 96 using the Abbott RealTime HIV-1 assay, blinded to randomized allocation. The primary (composite) endpoint, *good HIV disease control* was defined as having no new WHO stage 4 events (or death) after randomization (other than oesophageal candidiasis/mucosal herpes

simplex virus infection), and CD4 cell count >250 cells/mm^3, and VL <10,000 copies/ml (or >10,000 copies/ml without major/minor PI resistance mutations) at the end of the trial. Of the 1837 patients assessed for eligibility for the EARNEST trial, 560 were excluded, and in the majority (n = 396) this was because of a viral load <400 copies/ml.

Sexual behaviour sub-study

We approached the last 100 participants of the EARNEST trial from two sites – the Infectious Diseases Institute (IDI) clinic and the Joint Clinical Research Centre (JCRC) in Kampala, Uganda and 79 of them agreed to participate in the sexual behaviour sub-study. Twenty-one participants declined for various reasons, but particularly the need for additional travel and time off work to be interviewed for the sub-study. The sexual behaviour sub-study recruited participants within two months of randomization to second-line treatment. All participants received regular sexual risk reduction counselling and education on safer sex practices throughout the trial. A standardized 26-question questionnaire was used to collect information on participants' sexual behaviours over the preceding six months at baseline (see supplementary appendix) and at 48 and 96 weeks of follow-up and was administered through face-to-face interviews by a trained trial Nurse Counsellor at baseline and during follow-up. Questions addressed sexual activity with main sexual partner, as well as other sexual partners. This included number of sexual partners in the last six months, and for each partner frequency of sexual contact, consistency of condom use in the last month (always, sometimes, never), HIV status disclosure to the main partner and other sexual partners, and having had sex in exchange for money. At each study visit, information was also sought about new partners, change in marital status, and desire for children. A main sexual partner was defined as a stable partnership – the majority of these were either married/cohabiting or had a stable girlfriend/boyfriend relationship. The main trial protocol was approved by ethics committees of all participating countries and the United Kingdom (ISRCTN: 37737787). The sub-study was approved by the scientific review committee of IDI, the JCRC Institutional review board, and the Uganda National Council for Science and Technology (SS 2514). All participants provided written informed consent for both the main EARNEST trial and for the sexual behaviour sub-study prior to enrolment.

Statistical analysis

A descriptive analysis of distribution of overall sexual behaviours and four risky sexual behaviours in particular, stratified by gender, was undertaken at baseline, at 48 and 96 weeks after switch to second-line ART. Only data from 96 weeks' follow-up are reported here. Risky sexual behaviours were defined as reporting one of the following over the preceding six months: (1) having one or more sexual partners other than the main sexual partner; (2) inconsistent condom use (defined as never or sometimes using condoms versus always) with main sexual partner, and also with other sexual partners; (3) receiving or paying money in exchange for sex; and (4) non-disclosure of HIV status to main partner and non-disclosure to other sexual partners. We examined changes in these behaviours between baseline and 96 weeks, using Pearson Chi square test or Fisher's exact test when appropriate in bivariate analyses by gender. To address implications of virological failure at 96 weeks on potential transmission of HIV and drug-resistant virus, we also examined risky sexual behaviours among those with and without evidence of virological failure (defined as VL >400 copies/ml) at 96 weeks. Data entry was performed using Epidata software version 3.1 and all statistical analyses were performed using STATA® version 13, Texas USA. For all analyses, statistical significance was defined by $p < 0.05$. Our hypothesis was that risky sexual behaviours would improve over time following being switched to second-line ART.

Results

Overall, 79 participants were enrolled from two sites (JCRC and IDI) in Uganda. Table 1 summarizes the baseline demographic, clinical characteristics, and sexual behaviours overall and in men and women. Forty-nine (62%) participants were female, median age was 37 years (IQR: 32–42), median CD4 cell count was 79 cells/μl (IQR: 50–153), and median VL was 4.9 $\log_{10}$ copies/ml (IQR: 4.5–5.3). The median duration of first-line ART at time of enrolment was 3.7 years IQR (2.7–4.96), and the most common regimens taken before enrolment were lamivudine/stavudine/nevirapine (35.1%) and lamivudine/stavudine/efavirenz (28.6%). The majority (65%) were in a stable married or a cohabiting relationship and had a median of three living children. The majority (72%) of participants also self-reported that they felt that they had insufficient financial resources for their needs this (included response categories of 'not at all' or 'a little'), and this was similar between men and women. However, there was a marked gender difference in financial dependence. More than 70% of women reported that they were either completely or partially financially dependent compared to only 13.3% of men ($p < 0.001$).

Table 1. Demographic, clinical characteristics, and sexual behaviours at baseline on initiation of second-line ART in 79 EARNEST trial participants enrolled in a sexual behaviour sub-study, stratified by gender.

Characteristic	Total n = 79	Male n = 30	Female n = 49	p-value (male versus female)
	No (%) or median and IQR			
Demographic characteristics				
Age in years, median (IQR)	37 (32–42)	37 (34–42)	36 (31–42)	0.228
Marital status				
Not married	30/79 (38)	8/30 (26.7)	22/49 (44.9)	0.105
Married or cohabiting	49/79 (62)	22/30 (73.3)	27/49 (55.1)	
Desire to have more children	34/79 (43)	19/30 (63.3)	15/49 (30.6)	0.004
Number of living children median (IQR)	3 (2–5)	3 (2–4)	3 (2–4)	0.197
Self-assessed financial status				
Independent	40/79 (50.6)	26/30 (86.7)	14/49 (28.6)	<0.001
Partly dependent	24/79 (30.4)	4/30 (13.3)	20/49 (40.8)	
Completely dependent	15/79 (19)	–	15/49 (30.6)	
Self-assessed 'Has enough money to meet needs'				
Not all	12/79 (15.2)	3/30 (10)	9/49 (18.4)	0.476
A little	45/79 (57)	17/30 (56.7)	28/49 (57.1)	
Moderately	21/79 (25.6)	9/30 (30)	12/49 (24.5)	
Completely	1/79 (1.2)	1/30 (3.3)	–	
Clinical characteristics				
BMI (kg/m^2) median (IQR)		(n = 29)	(n = 48)	
<18.5	19/77 (24.7)	7/29 (24.1)	12/48 (25)	0.932
≥18.5	58/77 (75.3)	22/29 (75.9)	36/48 (75)	
CD4 cell count/μl, median (IQR)	79 (50–153)	74 (38–107)	88 (53–184)	0.097
HIV RNA log copies/ml, median (IQR)	4.9 (4.5–5.3)	5.1 (4.7–5.4)	4.8 (4.4–5.2)	0.073
Randomized second-line ART				
Standard of care (Boosted PI[a] plus 2/3 NRTIs [PI/NRTI])	26/79 (32.9)	11/30 (36.7)	15/49 (30.6)	0.648
Boosted PI/raltegravir[a]	26/79 (32.9)	8/30 (26.6)	18/49 (36.7)	
Boosted PI monotherapy after 12-week raltegravir induction (PI monotherapy)	27/79 (34.2)	11/30 (36.7)	16/49 (36.7)	
General sexual behaviour	(n = 79)	(n = 30)	(n = 49)	
Has main sexual partner	55/79 (69.6)	25/30 (83.3)	30/49 (61.2)	0.001
Nature of relationship with main partner	(n = 55)	(n = 25)	(n = 30)	
Husband/wife	40/55 (72.7)	20/25 (80)	20/30 (66.7)	0.232
Girlfriend/boyfriend	12/55 (21.8)	3/25 (12)	9/30 (30)	
Casual acquaintance	2/55 (3.6)	1/25 (4)	1/30 (3.3)	
Commercial sex partner	1 (1.8)	1/25 (4)	0	
Duration of relationship with main partner				
≤6 months	8/55 (14.5)	5/25 (20)	3/30 (10)	0.781
6–12 months	3/55 (5.5)	1/25 (4)	2/30 (6.7)	
1–2 years	7/55 (12.7)	3/25 (12)	4/30 (13.3)	
>2 years	37/55 (67.3)	16/25 (64)	21/30 (70)	
Sexual activity with main partner in last six months	48/55 (87.3)	22/25 (88)	26/30 (86.7)	0.604
Number of times had sex in last month	(n = 48)	(n = 22)	(n = 26)	
1–2	25/48 (52.1)	11/22 (50)	14/26 (53.8)	0.790
≥3	23/48 (47.9)	11/22 (50)	12/26 (46.2)	

(continued)

Table 1. Continued.

Characteristic	Total n = 79	Male n = 30	Female n = 49	p-value (male versus female)
	No (%) or median and IQR			
How often condoms were used				
Never	10/48 (20.8)	6/22 (27.3)	4/26 (15.4)	0.560
Sometimes	14/48 (29.2)	5/22 (22.7)	9/26 (34.6)	
Always	24/48 (50)	11/22 (50)	13/26 (50)	
Non-disclosure of HIV status	(n = 55)	(n = 25)	(n = 30)	
Non-disclosure of HIV status to main sexual partner	24/55 (43.6)	10/25 (41.7)	14/30 (45.2)	0.796
Non-disclosure of HIV status by main sexual partner	22/55 (40)	9/25 (37.5)	13/30 (41.9)	0.739
Sexual activity with other partners in last six months	n = 55	n = 25	n = 30	
Had other sexual partners in addition to main partner	11/55 (20.3)	9/25 (36)	2/30 (6.7)	<0.001
How many other sexual partners	(n = 11)	(n = 9)	n = 2	
1	8/11 (72.7)	6/9 (66.7)	2/2 (100)	0.632
≥2	3/11 (27.3)	3/9 (33.3)	–	
Non-disclosure of HIV status to other sexual partners	8/11 (72.7)	6/9 (66.7)	2/2 (100)	0.509
Inconsistent (i.e. never or sometimes) condom use with other partners	5/11 (45.5)	3/9 (33.3)	2/2 (100)	0.087
Summary of risky sexual behaviours in last six months				
Had other sexual partners in addition to main partner	11/55 (20)	9/25 (36)	2/30 (6.7)	<0.001
Inconsistent condom use with main sexual partner[b]	24/48 (50.0)	11/22 (50.0)	13/26 (50.0)	0.584
Inconsistent condom use with other sexual partner(s)[b]	5/11 (45.5)	3/9 (33.3)	2/2 (100)	0.087
Received or paid money in exchange for sex	14/79 (17.7)	3/30 (10)	11/49 (22.4)	0.013
Non-disclosure of HIV status to main partner	24/55 (43.6)	10/30 (40)	14/31 (45.2)	0.796
Non-disclosure of HIV status to other sexual partners	8/11 (72.7)	6/9 (66.7)	2/2 (100)	0.509

[a]bPI – boosted PI (lopinavir/ritonavir 400 mg/100 mg twice daily), with either 2–3 new or recycled NRTIs chosen, without genotyping, by the treating doctor; orraltegravir 400 mg twice daily, or PI monotherapy.
[b]Inconsistent condom use includes never or only sometimes use of condoms in last six months.
Denominators vary for different variables, and include n = 79 (total study population); n = 55 (those with main sexual partner); n = 48 (those with main sexual partner and sexually active in last six months); n = 11 (those reporting other sexual partners in last six months).

Sexual behaviours at initiation of second-line ART

Main sexual partner: The majority (69.6%, n = 55) reported that they had a main sexual partner, and 87.3% of these reported that they had been sexually active in the preceding six months. In 67.3%, this relationship had been for at least two or more years. Fifty per cent reported inconsistent condom use (i.e. never used [20.8%] or only sometimes used [29.2%] a condom) with the main partner. There was also a high rate of mutual non-disclosure of HIV status both to main sexual partner 24/55 (43.6%) and from main partners 22/55 (40%).

Other sexual partners: Eleven persons (20%) (nine men and two women) out of the 55 who had a main partner reported that they had sexual partners other than the main partner over the preceding six months. Eight participants had one other partner and three reported having two or more other sexual partners in addition to their main sexual partner. Overall, five of these 11 (45.5%) reported inconsistent condom use and 8/11 (72.7%) had not disclosed their HIV status to their other sexual partner. Fourteen of 79 participants (17.7%) (three men and 11 women) reported having received or paid money in exchange for sex in the preceding six months.

Overall, the majority of clinical characteristics and sexual behaviours were similar in men and women. Distinct differences by gender were that male participants were more likely to be married or cohabiting (73.3% versus 55.1%, $p = 0.105$), financially independent (86.7% versus 28.6%, $p < 0.001$), have a desire to have more children (63.3% versus 30.6%, $p = 0.004$), and to have sexual partners other than the main partner (36% versus 6.7%, $p < 0.001$). Females, however, were more likely to have exchanged money for sex (22.4% versus 10%, $p = 0.013$).

Trends in key sexual behaviours at 96 weeks after switch to second-line ART

Table 2 shows trends in key sexual behaviours overall and according to gender at 96 weeks after switch to second-line ART. Five (6.3%) participants died before 96 weeks and five (6.3%) were lost to follow-up. Overall sexual behaviours remained relatively stable during follow-up, although this was based on small numbers for individual sexual behaviours according to gender. The majority of those with a main sexual partner 46/69 (66.7%) at 96 weeks were sexually active 41/46 (89.1%) over this period. The proportion with no sexual partners was similar at baseline (24/79 [30.4%]) and 96 weeks (23/69 [33.3%]). There was a significant reduction in percentage of non-disclosure of HIV status to main sexual partner at baseline (24/55 [43.6%]) and during follow-up 9/46 (19.6%) ($p = 0.002$), and this was the case for both men and women.

There were several other observed trends over time. First, at 96 weeks the proportion of women who reported that they were now financially completely dependent significantly decreased from 30.6% at baseline to 17.5% at 96 weeks ($p < 0.001$), while men maintained a high level of financial independence both at baseline (87%) and at 96 weeks (100%). Desire to have more children significantly increased only among men from (19/30) 63.3% at baseline to (24/29) 82.7% at 96 weeks ($p < 0.001$).

In terms of changes in risky sexual behaviours during follow-up – the 24 people who had not disclosed to their main partner and the eight to other sexual partners at baseline subsequently disclosed during their follow-up visits. Seven of 11 people who had multiple sexual partners at baseline were still in the same relationships at 96 weeks. Two men reported having had multiple sexual partners at all visits.

Immunological and virological outcomes

There was substantial increase in median CD4 cell count between baseline and 96 weeks: females from 88 cells/μl (IQR: 53–184) to 356 cells/μl (IQR: 267–431) and from 74 cells/μl (IQR: 38–107) to 287 cells/μl (IQR: 225–352) for males. At 96 weeks, 16 participants had evidence of virological failure (six male and ten female). Of these, eight (50%) were sexually active, none had other sexual partners, four (25%) reported inconsistent condom use with main partner, and only one person (12.5%) had never disclosed his HIV status. At 96 weeks, six (37.5%) participants of those with virological failure (three female/three male) had evidence of drug resistance. The three male participants were all sexually active, had never had other partners, had disclosed their status to their main partners but two (66.7%) of them reported inconsistent condom use with their main partners. The three female participants with drug resistance had not been sexually active in the preceding six months.

Discussion

This is one of the first longitudinal studies to report on patterns of sexual behaviour and, in particular, prevalence of risky behaviours in persons failing first-line ART and the impact on risky sexual behaviours following a switch to second-line ART over 96 weeks of follow-up. Our sexual behaviour study was a small observational sub-study as part of the large randomized second-line ART EARNEST trial across five sub-Saharan African countries.[26] Overall, EARNEST trial participants were broadly representative of those failing ART regimens in the country as there were limited options for VL measurement and switching to a second-line treatment regimen at the time. The sub-study population from the two sites in Uganda was similar to the overall EARNEST trial of 1200 participants: 62% were female with a median age of 37 years and a CD4 cell count of 79 cells/μl,[26] as well as to a multicentre cohort study of more than 80,000 persons initiating ART across three countries in East Africa.[27] More than 70% reported that they did not have sufficient money for their needs reflecting the very low income status of persons living with HIV in this setting.

There were several key findings. First, the majority were in long-term stable relationships (defined as main partnerships) and were sexually active. Second, around 20% had other sexual partners, and this was six times higher among men than women. Third, in 50% there was inconsistent condom use with both their main sexual partners but also with other sexual partners, both at baseline and during follow-up. Fourth, around 40% of participants had not disclosed their HIV status to their main sexual partner (73% to other sexual partners) at the time of diagnosis of treatment failure and study enrolment, which was similar in men and women. However, there was a statistically significant reduction in non-disclosure among both males

Table 2. Change in key sexual behaviours and sexual risk behaviours for males and females between baseline and 96 weeks after switch to second-line ART.

	Baseline (n = 79)			96 weeks (n = 69)				
Variable	Total, N(%)	Male, n(%)	Female, n(%)	Total, N(%)	Male, n(%)	Female, n(%)	p-value Males Baseline versus 96 weeks	p-value Females Baseline versus 96 weeks
Had main sexual partner in last six months	55/79 (69.6)	25/30 (83.3)	30/49 (61.2)	46/69 (66.7)	22/29 (75.9)	24/40 (60)	0.426	0.906
Had sex with main partner in last six months	48/55 (87.3)	22/25 (88)	26/30 (86.7)	41/46 (89.1)	22/22 (100)	19/24 (79.2)	0.604	0.355
Risky sexual behaviour								
Had other sexual partners in last six months	11/55 (20.3)	9/25 (36)	2/30 (6.7)	7/46 (15.2)	5/22 (22.7)	2/24 (8.3)	0.095	0.399
Inconsistent condom use with main partner	24/48 (50.0)	11/22 (50.0)	13/26 (50.0)	23/41 (56.1)	13/22 (59.1)	10/19 (52.6)	0.753	0.862
Inconsistent condom use with other partners	5/11 (45.5)	3/9 (33.3)	2/2 (100)	3/7 (42.9)	3/5 (60)	0/2 (0)	0.400	0.167
Non-disclosure of HIV status to main sexual partner and during follow-up to new sexual partners	24/55 (43.6)	10/25 (40)	14/30 (46.7)	9/46 (19.6)	4/22 (18.2)	5/24 (20.8)	0.006	0.048
Received or paid money in exchange for sex	14/79 (17.2)	3/30 (10)	11/49 (22.4)	–	–	–	–	–
Financial status								
Completely independent	40/79 (50.6)	26/30 (86.7)	14/49 (28.6)	46/69 (66.7)	29/29 (100)	17/40 (42.5)	0.896	0.170
Partly dependent	24/79 (30.4)	4/30 (13.3)	20/49 (40.8)	16/69 (23.2)	–	16/40 (40)	–	0.938
Completely dependent	15/79 (19.0)	–	15/49 (30.6)	7/69 (10.1)	–	7/40 (17.5)	–	<0.001
Desire to have more children	34/79 (43.0)	19/30 (63.3)	15/49 (30.6)	41/69 (59.4)	24/29 (82.7)	17/40 (42.5)	<0.001	0.173

[a]There were 79 participants at baseline. Five participants died and five were lost to follow-up during the study resulting in 69 participants evaluated at 96 weeks.

and females over the 96 weeks of follow-up. There was no other significant change in sexual behaviours over the 96 weeks of follow-up after switch to second-line ART. Fifth, there were several important gender differences. Men were more likely to be married or cohabiting, financially independent, desired to have more children, and to have other sexual partners other than their main partner compared to women.

Overall, the findings are broadly consistent with other data on sexual behaviours from sub-Saharan Africa. Similar high rates of non-disclosure of HIV status to sexual partners (between 66 and 88% to main sex partners and 25 and 58% to casual partners) were reported in a review of studies in sub-Saharan Africa by Sullivan.[28] Factors reported to be associated with self-disclosure in other studies include support from the partner, ability to communicate about safe sex including telling or asking about one's or partner's sero-status.[28] In contrast, non-disclosure of HIV status to partners has been linked to previous experiences of HIV stigma and discrimination of PLHIV,[29,30] gender-based violence,[31] negative outcomes from previous disclosure experiences,[32] and a larger social context that promotes concealment of HIV status.[31] We observed that around 18% of participants received or paid money in exchange for sex, which is broadly consistent with the 10% reported from a Demographic Health Survey data of 12 African countries,[33,34] as well as two earlier studies from sub-Saharan Africa.[35,36] Consistent with our findings, other studies also show that women engage in provision of sexual services in exchange for money or other benefits, referred to as a transactional sex, more often than their male counterparts.[37–39] Other gender differences in our findings have also been reported elsewhere. A population-based study from Uganda showed that men were likely to have other partners than women, and in most cases the HIV status of other partners was unknown.[40] A further study from Kenya among 15- to 29-year-olds found that 11% of married men and 3% of married women had other sexual partners other than the main one.[41] Our finding that almost twice as many male participants expressed a desire to have more children is also consistent with earlier work in South Africa, Nigeria, Malawi, Kenya, and Uganda.[42–48] A survey conducted in south-western Uganda showed that women living with HIV had lower desire for future children, irrespective of whether they were on ART or not, than HIV-negative women.[49]

There are several limitations to our study. First, it was based on a relatively small sample size of 79 persons (49 women and 30 men, which is less than 10% of the EARNEST study population) and only 69 over the full 96 weeks of follow-up. This limits the interpretation of trends in sexual behaviour, especially when stratified by gender. Second, our study relied on self-reported sexual behaviours elicited by the EARNEST trial nurses who also provided ongoing risk reduction counselling to the sub-study participants, which may have led to under-reporting of sexual risk behaviours.[50] More in-depth qualitative interviews would have been helpful in providing insights into patients' motivations and helped triangulate the information obtained in this study.[51]

What are the implications of the high rates of inconsistent condom use and having other sexual partners, especially among men, for counselling and behavioural strategies? This is particularly relevant to sub-Saharan Africa where more than two-thirds of new HIV infections occur among heterosexual, stable relationships usually through risky sexual behaviour by one primary partner with a third person.[52,53] A key positive finding of our study is that during follow-up an increasing number of participants disclosed their HIV status to their partners. The ongoing counselling and encouragement to disclose by the study counsellors are likely to have played an important role, and this reinforces the importance of ongoing counselling. This is particularly important in those failing treatment who present a higher risk of transmission of not just HIV in the setting of a sustained high viral load but of drug-resistant virus. Of the 16 participants in this study who failed second-line ART with detectable VL, six had evidence of drug resistance. Of these, two men had high-risk sexual behaviours throughout study follow-up including multiple sexual partners and inconsistent condom use. Such persons need to be identified early and targeted for intensive counselling. Disclosure of partner's HIV status also would allow opportunities for self-testing and for short-term use of pre-exposure prophylaxis to prevent acquisition during the high-risk period before control of viraemia.[54–56]

With the continued scale up of access to VL monitoring of those on ART, there will be earlier diagnosis of treatment failure.[57] However, there remains in many countries high rates of ART drug resistance.[5,58] WHO has recently developed a five-year global action plan for 2017–2021 to support a coordinated international effort to prevent, monitor, and respond to the emergence of HIV drug resistance and to strengthen country efforts to achieve the global HIV targets.[59] There is need to intensify sexual risk reduction counselling and promotion of partner testing and disclosure, and reduce concurrent sexual partnerships, especially at diagnosis of treatment failure and after switch to second- or third-line ART. Several behavioural interventions have been developed to address sexual concurrency through comprehensive HIV prevention strategies in communities.[60–62]

Acknowledgements

We thank all the study participants and staff from the two centres participating in the EARNEST Sexual Behaviour substudy.

The EARNEST Trial Team at IDI, Kampala were G Bihabwa, E Buluma, P Easterbrook, A Elbireer, A Kambugu, D Kamya, M Katwere, R Kiggundu, C Komujuni, E Laker, E Lubwama, I Mambule, J Matovu, A Nakajubi, J Nakku, R Nalumenya, L Namuyimbwa, F Semitala, B Wandera, J Wanyama.

And at JCRC Kampala were: E Agweng, P Awio, G Bakeinyaga, C Isabirye, U Kabuga, S Kasuswa, M Katuramu, C Kityo, F Kiweewa, H Kyomugisha, E Lutalo, P Mugyenyi, D Mulima, H Musana, G Musitwa, V Musiime, M Ndigendawan, H Namata, J Nkalubo, P Ocitti Labejja, P Okello, P Olal, G Pimundu, P Segonga, F Ssali, Z Tamale, D Tumukunde, W Namala, R Byaruhanga, J Kayiwa, J Tukamushaba.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The EARNEST trial was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP, Grant Code: IP.2007.33011.003) with contributions from the Medical Research Council, UK, Institito de Salud Carlos III, Spain (Grant A107/90015), Irish Aid, Ireland, Swedish International Development Cooperation Agency (SIDA), Sweden, Instituto Superiore di Sanita (ISS), Italy and Merck, USA. Substantive in-kind contributions were made by the Medical Research Council Clinical Trials Unit, UK, CINECA, Bologna, Italy, Janssen Diagnostics, Beerse, Belgium; GSK/ViiV Healthcare Ltd., UK; Abbott Laboratories, USA. Trial medication was donated by AbbVie, Merck, Pfizer, GSK and Gilead. The Malawi-Liverpool-Wellcome Trust Clinical Research Programme, University of Malawi College of Medicine receives core funding from the Wellcome Trust UK. We received funding for study participants' transport from the Directorate General for Development Cooperation (DGDC) through the Flemish Interuniversity council (VLIR-UOS).

References

1. Joint United Nations Programme on HIV/AIDS(UNAIDS). Global AIDS update 2016, http://www.unaids.org/en/resources/documents/2016/Global-AIDS-update-2016 (accessed 8 July 2016).
2. Gilks CF, Crowley S, Ekpini R, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. *Lancet* 2006; 368: 505–510.
3. Manasa J, Lessells RJ, Skingsley A, et al. High-levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa. *PLoS One* 2013; 8: e72152.
4. UNAIDS. Global HIV Statistics. Fact sheet November 2016. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (accessed 10 January 2016).
5. WHO. Global report on early warning indicators of HIV drug resistance 2016. Available at: http://www.who.int/hiv/pub/drugresistance/ewi-hivdr-2016/en/ (2016, accessed 22 October 2016).
6. Venkatesh KK, Flanigan TP and Mayer KH. Is expanded HIV treatment preventing new infections? Impact of antiretroviral therapy on sexual risk behaviours in the developing world. *AIDS* 2011; 25: 1939–1949.
7. Eisele T, Mathews C, Chopra M, et al. High levels of risk behavior among people living with HIV initiating and waiting to start antiretroviral therapy in Cape Town South Africa. *AIDS Behav* 2008; 12: 570–577.
8. Kaida A, Gray G, Bastos F, et al. The relationship between HAART use and sexual activity among HIV-positive women of reproductive age in Brazil, South Africa, and Uganda. *AIDS Care* 2008; 20: 21–25.
9. Sarna A, Luchters SM, Geibel S, et al. Sexual risk behaviour and HAART: a comparative study of HIV-infected persons on HAART and on preventive therapy in Kenya. *Int J STD AIDS* 2008; 19: 85–89.
10. Moatti J, Prudhomme J, Traore DC, et al. Access to antiretroviral treatment and sexual behaviours of HIV-infected patients aware of their serostatus in Côte d'Ivoire. *AIDS* 2003; 17: S69–S77.
11. Bateganya M, Colfax G, Shafer LA, et al. Antiretroviral therapy and sexual behavior: a comparative study between antiretroviral- naive and -experienced patients at an urban HIV/AIDS care and research center in Kampala, Uganda. *AIDS Patient Care STDs* 2005; 19: 760–768.
12. Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS* 2006; 20: 85–92.
13. Venkatesh KK, Srikrishnan AK, Safren SA, et al. Sexual risk behaviors among HIV-infected South Indian couples in the HAART era: implications for reproductive health and HIV care delivery. *AIDS Care* 2011; 23: 722–733.
14. Marcellin F, Bonono CR, Blache J, et al. Higher risk of unsafe sex and impaired quality of life among patients not receiving antiretroviral therapy in Cameroon: results from the EVAL survey (ANRS 12–116). *AIDS* 2010; 24: S17–S25.
15. Dia A, Marcellin F, Bonono R-C, et al. Prevalence of unsafe sex with one's steady partner either HIV-negative or of unknown HIV status and associated determinants in Cameroon (EVAL ANRS12–16 survey). *Sex Transm Infect* 2010; 86: 148–154.
16. Venkatesh K, de Bruyn G, Lurie MN, et al. Sexual risk behaviors among HIV-infected South African men and women with their partners in a primary care program: implications for couples-based prevention. *AIDS Behav* 2012; 16: 139–150.

17. Apondi R, Bunnell R, Ekwaru JP, et al. Sexual behaviour and HIV transmission risk of Ugandan adults taking antiretroviral therapy. 3 years follow-up. *AIDS* 2011; 25: 1317–1327.
18. McClelland R, Graham SM, Richardson BA, et al. Treatment with antiretroviral therapy is not associated with increased sexual risk behavior in Kenyan female sex workers. *AIDS* 2010; 24: 891–897.
19. Venkatesh K, de Bruyn G, Lurie MN, et al. Decreased sexual risk behavior in the era of HAART among HIV-infected urban and rural South Africans attending primary care clinics. *AIDS* 2010; 24: 2687–2696.
20. Peltzer K and Ramlagan S. Safer sexual behaviours after 1 year of antiretroviral treatment in KwaZulu-Natal, South Africa: a prospective cohort study. *Sexual Health* 2010; 7: 135–141.
21. Luchters S, Sarna A, Geibel S, et al. Safer sexual behaviors after 12 months of antiretroviral treatment in Mombasa, Kenya: a prospective cohort. *AIDS Patient Care STDs* 2008; 22: 587–594.
22. Wanyama J, Kasibante D, Kayiira P, et al. Sexual behavior of HIV+ persons before and after 1 year of ART at the Infectious Diseases Clinic, Kampala, Uganda. In: *Seventeenth conference on retroviruses and opportunistic infections*, San Francisco, 2010.
23. Diabaté S, Alary M and Koffi CK. Short-term increase in unsafe sexual behaviour after initiation of HAART in Côte d'Ivoire. *AIDS* 2008; 22: 154–156.
24. Kennedy C, O'Reilly K, Medley A, et al. The impact of HIV treatment on risk behaviour in developing countries: a systematic review. *AIDS Care* 2007; 19: 707–720.
25. Berhan A and Berhan Y. Is the sexual behaviour of HIV patients on antiretroviral therapy safe or risky in sub-Saharan Africa? Meta-analysis and meta-regression. *AIDS Res Ther* 2012; 9: 14.
26. Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med* 2014; 371: 234–247.
27. Nakanjako D, Kiragga A, Musick B, et al. Frequency and impact of sub-optimal immune recovery on first-line antiretroviral therapy within East African IeDEA cohort. *AIDS* 2016; 30: 1913–1922.
28. Sullivan KM. Male self-disclosure of HIV positive serostatus to sex partners: a review of the literature. *J Assoc Nurses AIDS Care* 2005; 16: 33–65.
29. UNAIDS. 2016 Core Epidemiology Slides. Available at: http://aidsinfo.unaids.org/ (2016, accessed June 2016).
30. Kalichman SC and Simbayi L. HIV testing attitudes, AIDS stigma and voluntary HIV counseling and testing in a Black township in Cape Town, South Africa. *Sex Transm Infect* 2003; 79: 442–447.
31. Kalichman SC and Simbayi LC. Traditional beliefs about the cause of AIDS and AIDS-related stigma in South Africa. *AIDS Care* 2004; 16: 573–581.
32. Dunkle KL, Jewkes RK, Brown HC, et al. Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. *Lancet* 2004; 363: 1415–1421.
33. Chatterji M, Murray N, London D, et al. The factors influencing transactional sex among young men and women in 12 sub-Saharan African countries. *Soc Biol* 2005; 52: 56–72.
34. Duffy L. Culture and context of HIV prevention in rural Zimbabwe: the influence of gender inequality. *J Transcult Nurs* 2005; 16: 23–31.
35. Moore AM, Biddlecom AE and Zulu EM. Prevalence and meanings of exchange of money or gifts for sex in unmarried adolescent sexual relationships in sub-Saharan Africa. *Afr J Reprod Health* 2007; 11: 44–61.
36. UN. *Women out loud: How women living with HIV will help the world ends AIDS, in United Nations Joint Programme on HIV/AIDS*. Geneva, Switzerland: Joint United Nations Program on HIV/AIDS (UNAIDS), 2012.
37. Vandepitte J, Lyerla R, Dallabetta G, et al. Estimates of the number of female sex workers in different regions of the world. *Sex Transm Infect* 2006; 82(Suppl 3): iii18–iii25.
38. Balmer DH, Gikundi E, Billingsley MC, et al. Adolescent knowledge, values, and coping strategies: implications for health in sub-Saharan Africa. *J Adolesc Health* 1997; 21: 33–38.
39. Kasamba I, Sully E, Weiss HA, et al. Extraspousal partnerships in a community in rural Uganda with high HIV prevalence: a cross-sectional population-based study using linked spousal data. *J Acquir Immune Defic Syndr* 2011; 58: 108–114.
40. Voeten HA, Egesah OB and Habbema JD. Sexual behavior is more risky in rural than in urban areas among young women in Nyanza province, Kenya. *Sex Transm Dis* 2004; 31: 481–487.
41. Snow R, Mutumba M, Powers G, et al. The impact of HIV on fertility aspirations in Uganda. Population Study Center Research Report 11-740, May 2011, p.19.
42. Beyeza-Kashesya J, Ekstrom AM, Kaharuza F, et al. My partner wants a child: a cross-sectional study of the determinants of the desire for children among mutually disclosed sero-discordant couples receiving care in Uganda. *BMC Public Health* 2010; 10: 247.
43. Nakayiwa S, Abang B, Packel L, et al. Desire for children and pregnancy risk behavior among HIV-infected men and women in Uganda. *AIDS Behav* 2006; 10: S95–104.
44. Awiti Ujiji O, Ekstrom AM, Ilako F, et al. "I will not let my HIV-status stand in the way." Decisions on motherhood among women on ART in a slum in Kenya – a qualitative study. *BMC Women's Health* 2010; 10: 13.
45. Cooper D, Harries J, Myer L, et al. "Life is still going on": reproductive intentions among HIV-positive women and men in South Africa. *Soc Sci Med* 2007; 65: 274–283.
46. Smith DJ and Mbakwem BC. Life projects and therapeutic itineraries: marriage, fertility, and antiretroviral therapy in Nigeria. *AIDS* 2007; 21: S37–41.
47. Yeatman S. HIV infection and fertility preferences in rural Malawi. *Stud Fam Plann* 2009; 40: 261–276.
48. Shattuck D, Kerner B, Gilles K, et al. Encouraging contraceptive uptake by motivating men to communicate about family planning: the Malawi male motivator project. *Am J Public Health* 2011; 101: 1089–1095.
49. Maier M, Andia I, Emenyonu N, et al. Antiretroviral therapy is associated with increased fertility desire, but

not pregnancy or live birth, among HIV positive women in an early HIV treatment program in rural Uganda. *AIDS Behav* 2009; 13: 28–37.
50. Schroder KE, Carey MP and Vanable PA. Methodological challenges in research on sexual risk behavior: II. *Accuracy of self-reports*. Ann Behav Med 2003; 26: 104–123.
51. Phillips AE, Gomez GB, Boily M-C, et al. A systematic review and meta-analysis of quantitative interviewing tools to investigate self-reported HIV and STI associated behaviours in low- and middle-income countries. *Int J Epidemiol* 2010; 39: 1541–1555.
52. Chemaitelly H, Awad SF, Shelton JD, et al. Sources of HIV incidence among stable couples in sub-Saharan Africa. *J Int AIDS Soc* 2014; 17: 18765.
53. Dunkle KL, Stephenson R, Karita E, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. *Lancet* 2008; 371: 2183–2191.
54. Atuyambe LM, Ssegujja E, Ssali S, et al. HIV/AIDS status disclosure increases support, behavioural change and, HIV prevention in the long term: a case for an Urban Clinic, Kampala, Uganda. *BMC Health Serv Res* 2014; 14: 276.
55. Simbayi LC, Kalichman SC, Strebel A, et al. Disclosure of HIV status to sex partners and sexual risk behaviours among HIV-positive men and women, Cape Town, South Africa. *Sex Transm Infect* 2007; 83: 29–34.
56. Kebede D, Kifle W, Mekitie W, et al. Disclosure experience and associated factors among HIV positive men and women clinical service users in southwest Ethiopia. *BMC Public Health* 2008; 8: 81.
57. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach-Second edition. June 2016. Available at: http://www.who.int/hiv/pub/arv/arv-2016/en/ (2016, accessed 22 June 2016).
58. The TenoRes Study Group. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multi-centre retrospective cohort study. *Lancet Infect Dis* 2016; 16: 565–575.
59. WHO. Global action plan for HIV drug resistance 2017–2021. Combating HIV drug resistance, a little known but growing threat (In press). Available at: http://apps.who.int/iris/bitstream/10665/255883/1/9789241512848-eng.pdf?ua=1 (2017, accessed 3 August 2017).
60. Knopf A, Agot K, Sidle J, et al. "This is the medicine": A Kenyan community responds to a sexual concurrency reduction intervention. *Soc Sci Med* 2014; 108: 175–178.
61. Wingood GM, Rubtsova A, DiClemente RJ, et al. A new paradigm for optimizing HIV intervention synergy: the role of interdependence in integrating HIV prevention interventions. *J Acquir Immune Defic Syndr* 2013; 63: S108–S113.
62. McCreesh N, O'Brien K, Nsubuga RN, et al. Exploring the potential impact of a reduction in partnership concurrency on HIV incidence in rural Uganda: A modeling study. *Sex Transm Dis* 2012; 39: 407–413.