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Sexual behaviour among people with HIV according to self-reported antiretroviral treatment and viral load status

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Objective: To assess, among people with HIV, the association of self-reported antiretroviral treatment (ART) and viral load status with condomless sex with an HIV-serodifferent partner (CLS-D).

Design: Cross-sectional study of 3258 HIV-diagnosed adults in the United Kingdom, 2011–2012.

Methods: CLS-D in the past 3 months and self-reported ART/viral load were ascertained by questionnaire. Clinic-recorded viral load was documented. HIV-transmission risk sex (CLS-D-HIV-risk) was defined as CLS-D together with either not on ART or clinic-recorded viral load more than 50 copies/ml.

Results: Of 3178 participants diagnosed more than 3 months ago, 2746 (87.9%) were on ART, of whom self-reported viral load was '50 copies/ml/ or less/undetectable' for 78.4%; 'more than 50 copies/ml/detectable' for 8.3%; 'do not know/missing' for 13.3%. CLS-D prevalence was 14.9% (326/2189), 6.4% (23/360) and 10.7% (67/629) among men who have sex with men, heterosexual men and women, respectively. Among men who have sex with men, CLS-D prevalence was 18.8% among those not on ART; 15.2% among those on ART with undetectable self-reported viral load; 9.8% among those on ART without undetectable self-reported viral load. Compared with 'on ART with undetectable self-reported viral load', prevalence ratios (95% confidence interval) adjusted for demographic/HIV-related factors were: 0.66 (0.45, 0.95) for 'on ART without undetectable self-reported viral load', and 1.08 (0.78, 1.49) for 'not on ART' (global $P = 0.021$). Among heterosexual men and women (combined), ART/self-reported viral load was not associated with CLS-D [corresponding adjusted prevalence ratios: 1.14 (0.73, 1.79) for 'on ART without undetectable self-reported viral load'; 0.88 (0.44, 1.77) for 'not on ART', $P = 0.77$]. CLS-D-HIV-risk prevalence was 3.2% among all participants; 16.1% for 'not on ART'; 0.6% for 'on ART with undetectable self-reported viral load; 4.2% for 'on ART without undetectable self-reported viral load.'

Conclusion: Use of ART was not associated with increased prevalence of CLS-D, and was associated with greatly reduced prevalence of HIV-transmission risk sex.

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Introduction

Transmission of HIV in the United Kingdom continues to be high among men who have sex with men (MSM) [1–3]. Among heterosexual men and women, transmission within the United Kingdom is also ongoing, despite a decline in overall number of new diagnoses because of migration patterns [1]. Although it is estimated that most new HIV infections in the United Kingdom are transmissions from people unaware that they have HIV [3,4], a significant proportion (an estimated 18% among MSM [3]) are transmissions from people already diagnosed, indicating that prevention issues in this group remain important. Understanding patterns of sexual behaviour according to antiretroviral treatment (ART) use among people diagnosed with HIV has implications for clinical care and public health.

Recommendations on when (at what $CD4^+$ cell count) an individual with HIV should start ART have shifted, over time, towards earlier initiation of ART. For some years, interest has focused on a strategy of offering ART to all people with HIV, from diagnosis, irrespective of $CD4^+$ cell count [4,5], and such a policy was recommended in the United States in 2012 [6]. Until very recently, the main impetus for this strategy was the potential impact on transmission, based on compelling results regarding the profound reduction in infectiousness to sexual partners for HIV-positive people taking ART with suppressed viral load [7–13], in particular from the HPTN052 trial in 2011 [12], and the recent PARTNER study [13]. In May 2015, landmark results of the international START trial demonstrated that earlier ART also confers clinical prognostic benefit to the individual [14]. Consequently, treatment guidelines worldwide are being changed to recommend immediate ART for all people diagnosed with HIV [15,16]. Such a strategy should reduce HIV-related morbidity, and reduce HIV transmission.

A longstanding question is whether taking ART may influence an individual's sexual behaviour. This question is becoming increasingly relevant, as knowledge about the protective effect of ART on HIV infectiousness becomes established and widespread. The 'Swiss statement' [17] in 2008 marked the first fundamental change in advice about 'safe sex' for HIV-positive people, asserting (with caveats) that an HIV-positive person on ART with viral suppression is not sexually infectious. Subsequent results from the Swiss HIV Cohort study suggested higher levels of condomless sex (CLS) with stable partners of HIV-negative/unknown status among participants who were virally suppressed [18]. However, most studies carried out before [19–29] and soon after [30–33] the Swiss Statement have not found higher prevalence of CLS among people on ART or those with viral load suppression. There have been few studies of sexual behaviour among people with HIV in the United Kingdom since the Swiss statement, and none that have examined associations of CLS with *perceived* (self-reported) viral load status – the crucial measure when considering impact on behaviour.

If ART use or perceived suppressed viral load was found to be associated with substantially higher levels of condomless sex (CLS), this could undermine the full impact of early ART on HIV transmission. This could occur if individuals on ART were not accurately assessing their viral load status (and therefore infectiousness to sexual partners) and modifying sexual behaviour accordingly. Also of importance is that lower condom use among people on ART may have an adverse effect on transmission of sexually transmitted infections other than HIV (STIs), the infectivity of which would not be lessened by ART use. Occurrence of STIs is high among HIV-diagnosed MSM [34,35].

The Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study investigated sexual behaviour among people with HIV in the United Kingdom, and aimed to address the hypothesis that ART use and perceived undetectable viral load may be linked to CLS. This report assesses the association of self-reported ART/viral load status with CLS, in particular CLS with an HIV-serodifferent partner. In addition, as the protective effect of suppressed viral load on HIV infectiousness is now known with confidence, this report is the first to describe likely levels of CLS carrying an appreciable risk of HIV transmission (accounting for clinic-documented viral load level) according to self-reported ART/viral load. Although attitudes and behaviour in relation to condom use may be changing rapidly, as knowledge about transmission risk is disseminated and develops, the ASTRA results will also be important in establishing a baseline against which findings of future studies of HIV-positive people can be evaluated.

Methods

ASTRA recruited adults with diagnosed HIV attending eight hospital HIV outpatient clinics in the United Kingdom from February 2011 to December 2012. Full details have been described [36]. Participants self-completed a confidential sex-specific questionnaire on socio-demographic, HIV-related, health and lifestyle factors, and sexual behaviour. The latest documented viral load and $CD4^+$ cell count results that the participant had been informed of were collected from medical records. The study was approved by North West London REC 2 research ethics committee (ref 10/H0720/70). At the time of the study, the British HIV Association guidelines recommended ART initiation for HIV-positive people with a $CD4^+$ cell count of 350 cells/μl or less, unless special circumstances indicated earlier ART [37].

Self-reported antiretroviral treatment/viral load

Participants were asked about ever and current ART use. Those who ever started ART were asked their viral load at the last test, with three options: '50 copies/ml or less (undetectable or suppressed)'; 'more than 50 copies/ml (detectable or raised)' and 'don't know'. Self-reported ART/viral load was categorised into three groups: not on ART; on ART with undetectable self-reported viral load; on ART without undetectable self-reported viral load (including 'do not know' and missing self-reported viral load).

Sexual behaviour

The men's questionnaire asked about sex with women, and sex with men; the women's questionnaire asked about sex with men. Participants were asked whether, in the past 3 months, they had: anal or vaginal sex (and if so how many partners), sex without a condom (CLS), CLS with an HIV-positive person, CLS with an HIV-serodifferent (negative or unknown status) partner (CLS-D). Those reporting CLS-D were asked: number and type (long-term or other) of CLS-D partner(s); number of times had CLS-D (in categories); whether they ever ejaculated inside a partner during CLS-D (men only); position for anal CLS-D for MSM (always insertive; always receptive; both); reasons for not using a condom at last CLS-D (11 options including: 'I believe the risk of HIV transmission is very low'). Those who reported CLS, but did not indicate HIV status of partner(s), were classified as having 'possible CLS-D', but not included in the main definition. All participants were asked about group sex and new STI diagnoses in the past 3 months, and number of new sexual partners in the past year.

HIV-transmission risk sex

A variable was constructed to define sex with an appreciable risk of HIV transmission (CLS-D-HIV-risk). CLS-D-HIV-risk is a subset of CLS-D. An individual was positive for CLS-D-HIV-risk if, in addition to reporting CLS-D, they were either not on ART (self-reported) or had clinic-recorded viral load more than 50 copies/ml (using the single viral load documented for each participant). Individuals who reported CLS-D, but were on ART with clinic-recorded viral load 50 copies/ml or less were negative for CLS-D-HIV-risk.

Transmission risk beliefs

Participants rated their agreement (strongly agree, tend to agree, undecided/no opinion, tend to disagree and strongly disagree) with the following statements: 'An undetectable HIV viral load makes someone less infectious to a sexual partner than if they had a high viral load' and 'When viral load is undetectable, a condom is not needed to prevent HIV transmission'.

Statistical analysis

Individuals who reported an HIV diagnosis date less than 3 months before the date of questionnaire issue were excluded, to ensure reported sexual behaviour related to a period after diagnosis. Men who self-identified as gay or bisexual or reported sex with a man in the past 3 months were classified as MSM. Characteristics and sexual behaviour were summarised for: MSM, heterosexual men, women. Subsequent analyses were conducted separately for MSM and all heterosexual individuals. The combined heterosexual category was used to increase power; there was no evidence that associations differed between men and women. Unadjusted associations of self-reported ART/viral load and other factors with CLS-D, and CLS overall, were assessed using χ^2 tests. Modified Poisson regression [38] was used to obtain unadjusted and adjusted prevalence ratios with 95% confidence intervals (CI), for association of self-reported ART/viral load with CLS-D. First, adjustment was made for socio-demographic and HIV-related factors: age group ($<$30 years; $\geq$30 years); black ethnicity (no/missing; yes); university education (no/missing; yes); identifying with a religion (no/missing; yes); time with diagnosed HIV (3 months to 1.9 years; 2–4.9 years; 5–9.9 years; 10–14.9 years; 15–19.9 years; $\geq$20 years) and partner status (HIV-positive; HIV-negative/unknown status; no stable partner). Age was used in two categories only because of collinearity with time with diagnosed HIV. In a second model, additional adjustment was made for higher alcohol intake (no/missing; yes, using score $\geq$6 on the first two WHO AUDIT-C [39] questions) and number of recreational drugs used in the past 3 months (none/missing; 1; 2–3; $\geq$4) [40]. In heterosexual models, categories were collapsed for some variables (see Table 4) and there was additional adjustment for sex. Model results were not materially altered by further adjustment for clinic, or when cases that had been excluded because of missing values in age, diagnosis date, partner status or self-reported ART/viral load were included using 'missing' categories. The prevalence of CLS-D-HIV-risk was described overall, and for MSM, and heterosexual men and women, according to self-reported ART/viral load.

Three sensitivity analyses were performed separately for MSM and heterosexual individuals. The association of self-reported ART/viral load with CLS-D was assessed:

(a) including 'possible CLS-D' cases;
(b) excluding participants who reported no sex in the past 3 months;
(c) separately among those diagnosed with HIV for less than 5 years and 5 years or more.

Results

Overall, 3258 people with diagnosed HIV participated in ASTRA (5112 invited: response rate 64%), of whom 80 are excluded as they had been diagnosed for less than 3 months. Table 1 shows characteristics for the 3178 included participants (2189 MSM, 360 heterosexual men

Table 1. Characteristics of 3178 individuals diagnosed with HIV more than 3 months ago, according to gender/sexual orientation.

	MSM, $N=2189$	Heterosexual men, $N=360$	Women, $N=629$
$N=3178$	*n* (%)	*n* (%)	*n* (%)
Age group (years), $N=3112$			
<30	96 (4.4)	9 (2.6)	54 (9.1)
30–39	487 (22.5)	59 (16.9)	174 (29.2)
40–49	929 (42.9)	160 (45.7)	255 (42.9)
50–59	503 (23.2)	86 (24.6)	88 (14.8)
≥60	152 (7.0)	36 (10.3)	24 (4.0)
Ethnicity, $N=3178$[d]			
White	1931 (88.2)	113 (31.4)	123 (19.6)
Black African	21 (1.0)	179 (49.7)	401 (63.8)
Black other	54 (2.5)	25 (6.9)	44 (7.0)
Other/missing	183 (8.4)	43 (11.9)	61 (9.7)
UK birth, $N=3105$			
Yes	1532 (70.9)	96 (27.7)	112 (18.7)
No	629 (29.1)	250 (72.3)	486 (81.3)
Education, $N=3178$[d]			
University	954 (43.6)	129 (35.8)	195 (31.0)
Other/missing	1235 (56.4)	231 (64.2)	434 (69.0)
Employment status, $N=3097$			
Employed (full or part time)	1326 (61.6)	158 (46.1)	282 (47.0)
Unemployed	309 (14.3)	94 (27.4)	160 (26.7)
Not working because of sickness/disability	316 (14.7)	38 (11.1)	62 (10.3)
Other (student, looking after home, retired, other)	203 (9.4)	53 (15.5)	96 (16.0)
Money for basic needs? $N=3116$			
Always	1116 (51.6)	100 (28.8)	130 (21.5)
Mostly	597 (27.6)	79 (22.8)	147 (24.3)
Sometimes	277 (12.8)	101 (29.1)	178 (29.4)
No	173 (8.0)	67 (19.3)	151 (24.9)
Identifies with a religion, $N=3178$[d]			
Yes	934 (42.7)	282 (78.3)	551 (87.6)
No/missing	1255 (57.3)	78 (21.7)	78 (12.4)
Time with diagnosed HIV, $N=3150$			
3 months to 1.9 years	184 (8.5)	45 (12.7)	64 (10.4)
2–4.9 years	338 (15.5)	63 (17.7)	97 (15.7)
5–9.9 years	550 (25.3)	111 (31.3)	232 (37.5)
10–14.9 years	461 (21.2)	69 (19.4)	117 (18.9)
15–19.9 years	376 (17.3)	45 (12.7)	67 (10.8)
≥20 years	268 (12.3)	22 (6.2)	41 (6.6)
Partner status, $N=3154$			
HIV+ stable partner	512 (23.6)	111 (31.1)	123 (19.7)
HIV− or HIV-unknown status stable partner	674 (31.0)	133 (37.3)	220 (35.3)
No stable partner	987 (45.4)	113 (31.7)	281 (45.0)
Current smoker, $N=3178$[d]			
No/missing	1377 (62.9)	252 (70.0)	562 (89.4)
Yes	812 (37.1)	108 (30.0)	67 (10.7)
Higher alcohol consumption[a], $N=3178$[d]			
No/missing	1821 (83.2)	317 (88.1)	616 (97.9)
Yes	368 (16.8)	43 (11.9)	13 (2.1)
Number of recreational drugs used in past 3 months[b], $N=3178$[d]			
None/missing	1078 (49.2)	303 (84.2)	585 (93.0)
1	364 (16.6)	36 (10.0)	36 (5.7)
2–3	403 (18.4)	21 (5.8)	7 (1.1)
≥4	344 (15.7)	0 (0)	1 (0.2)
Self-reported ART status, $N=3125$			
Never taken ART	253 (11.7)	19 (5.4)	42 (6.9)
Stopped ART	34 (1.6)	5 (1.4)	26 (4.3)
On ART	1876 (86.7)	327 (93.2)	543 (88.9)
Self-reported viral load status, $N=2746$ on ART only			
50 copies/ml or less (undetectable or suppressed)	1569 (83.6)	201 (61.5)	384 (70.7)
More than 50 copies/ml (detectable or raised)	153 (8.2)	32 (9.8)	42 (7.7)
Do not know	135 (7.2)	76 (23.2)	90 (16.6)
Missing	19 (1.0)	18 (5.5)	27 (5.0)
Clinic-recorded viral load[c] (copies/ml), $N=3157$			
≤50	1694 (77.9)	281 (78.7)	486 (77.8)
>50	481 (22.1)	76 (21.3)	139 (22.2)

Table 1 (*continued*)

	MSM, $N=2189$	Heterosexual men, $N=360$	Women, $N=629$
$N=3178$	*n* (%)	*n* (%)	*n* (%)
Clinic-recorded $CD4^+$ cell count [c] (cells/μl), $N=3155$			
<200	77 (3.5)	38 (10.7)	34 (5.4)
200–349	240 (11.0)	80 (22.5)	86 (13.8)
350–499	538 (24.7)	80 (22.5)	154 (24.6)
≥500	1320 (60.7)	157 (44.2)	351 (56.2)

[a]Score of 6 or more on modified WHO AUDIT C questionnaire (using first two questions only).
[b]Participants selected from a list of 18 with 'other' option. Includes LSD, anabolic steroids, cannabis, cocaine, crack, codeine, methamphetamine, ecstasy, GHB, herion, ketamine, khat, mephedrone, morphine, opium, nitrites, amphetamine and recreational Viagra.
[c]Latest clinic-recorded value that participant had been informed of. Clinic viral load was median (IQR) of 10 (3–18) weeks prior to questionnaire.
[d]Number of missing values included ranges from 28 to 83.

and 629 women). The vast majority reported being on ART: 1876 (86.7%) MSM, 327 (93.2%) heterosexual men and 543 (88.9%) women, of whom 83.6, 61.5 and 70.7% respectively had undetectable self-reported viral load. These differences in self-reported viral load among participants on ART were primarily because of the higher proportion of heterosexual men (23.2%) and women (16.6%) than MSM (7.2%) who did not know their viral load status. A small proportion of participants ($n=65$; 2.0%) reported having stopped ART. Overall 696 (22.1%) participants (12.4% of those on ART) had clinic-recorded viral load more than 50 copies/ml using the study-documented viral load.

Sexual behaviour and association with self-reported antiretroviral treatment/viral load among men who have sex with men

Table 2 shows sexual behaviour among 2189 MSM. In the past 3 months, 1392 (63.6%) MSM had anal/vaginal sex (1360 with men only, 12 with women only and 20 with both men and women), the majority of whom had more than one partner, with over a quarter having 5 partners or more. Overall, 836 (38.2%) MSM reported CLS; 326 (14.9%) reported CLS-D. When 'possible CLS-D' was included, prevalence rose to 16.3% ($n=357$). Of MSM having CLS-D, most (57.5%) reported a single CLS-D partner, whereas approximately 14% had 5 or more CLS-D partners. For the majority (76.1%) of men reporting CLS-D, this was sex with partners other than, or in addition to, a long-term partner. Of men having CLS-D, less than a third reported insertive anal CLS-D with ejaculation inside a partner, and 40% reported receptive anal CLS-D only. MSM who reported CLS-D had higher prevalence of self-reported STI (22.4% vs. 8.7%) and group sex (45.1% vs. 16.4%) than those who did not, and CLS-D prevalence increased markedly with greater numbers of new sexual partners (Fig. 1).

Among 2163 MSM with information on self-reported ART/viral load, those on ART were *less* likely than those not on ART to report anal/vaginal sex (61.9% vs. 76.7%), CLS (36.9% vs. 48.4%) and CLS-D (14.3% vs. 18.8%) in the past three months, $P<0.05$ for all (χ^2 tests). MSM on ART were less likely than those not on ART to have: STI (9.9% vs. 16.7%) or group sex (19.6% vs. 28.6%) in the past three months, or 10 or more new partners in the past year (24.5% vs. 36.2%), $P<0.001$ for all. Among MSM on ART, CLS-D prevalence was higher among those with undetectable self-reported viral load than without (15.2% vs. 9.8%, $P=0.014$, Table 3a). However CLS-D prevalence among MSM not on ART (18.8%) was higher than for both 'on ART' groups. Table 3a also shows associations with other factors. Prevalence of CLS-D declined with older age, and with longer time since HIV diagnosis, and was higher among MSM without an HIV-positive stable partner. CLS-D was associated with higher alcohol consumption, and strongly with recreational drug use, but not with ethnicity, birth in the United Kingdom, education, employment status, financial hardship, religion, smoking status or $CD4^+$ cell count. Patterns of association were similar with all CLS.

After adjustment for socio-demographic and HIV-related factors, compared with MSM on ART with undetectable self-reported viral load, those on ART without undetectable self-reported viral load had significantly lower CLS-D prevalence [adjusted prevalence ratio (95% CI): 0.66 (0.45, 0.95)], whereas those not on ART had similar prevalence [1.08 (0.78, 1.49)] (Table 4a). Attenuation of this latter effect ('not on ART' vs. 'ART with undetectable self-reported viral load') was primarily because of adjustment for time with diagnosed HIV. The significant difference in CLS-D between the two 'on ART' groups persisted after additional adjustment for alcohol and recreational drug use (Table 4a).

Sexual behaviour and association with self-reported antiretroviral treatment/viral load among heterosexual men and women

Table 2 shows sexual behaviour among heterosexual men and women. Of 360 heterosexual men, 226 (62.8%), 83 (23.1%) and 23 (6.4%) reported vaginal/anal sex, CLS and CLS-D respectively in the past 3 months. Among the 629 women, corresponding numbers were: 316 (50.2%), 133 (21.1%) and 67 (10.7%). Inclusion of 'possible' CLS-D made little difference to prevalence. Patterns of sexual behaviour among heterosexual participants differed from MSM: the vast majority had sex with a single partner,

Table 2. Sexual behaviour according to gender/sexual orientation, among 3178 individuals diagnosed with HIV more than 3 months ago.

Sexual behaviour in past 3 months (*N*, denominator across all groups)[a]	MSM *N* = 2189	Heterosexual men *N* = 360	Women *N* = 629
	n (%)	*n* (%)	*n* (%)
Any anal or vaginal sex (*N* = 3178)	1392 (63.6%)[i]	226 (62.8)	316 (50.2)
Number of anal/vaginal sexual partners (*N* = 1827[c] who had sex)			
1	594 (44.7%)	194 (90.7%)	279 (98.2%)
2–4	379 (28.5%)	19 (8.9%)	5 (1.8%)
5–9	171 (12.9%)	1 (0.5%)	–
10–19	106 (8.0%)	–	–
≥20	79 (5.9%)	–	–
Number not given	63	12	32
Condomless sex (CLS) (*N* = 3178)	836 (38.2%)	83 (23.1%)	133 (21.1%)
95% confidence interval (CI)	(36.1%, 40.3%)	(18.8%, 27.8%)	(18.0%, 24.5%)
CLS with HIV serodifferent partner (CLS-D)	326 (14.9%)	23 (6.4)	67 (10.7)
95% confidence interval (CI)	(13.4%, 16.5%)	(4.1%, 9.4%)	(8.4%, 13.3%)
CLS-D including 'possible' cases[b]	357 (16.3%)	25 (6.9)	68 (10.8)
95% confidence interval (CI)	(14.8%, 17.9%)	(4.5%, 10.1%)	(8.5%, 13.5%)
Number CLS-D partners, (*N* = 403[d] who had CLS-D)			
1	180 (57.5)	21 (91.3)	67 (100.0)
2–4	90 (28.8)	2 (8.7)	–
5–9	22 (7.0)	–	–
≥10	21 (6.7)	–	–
Number not given	13	–	–
Total number times CLS-D, (*N* = 375[e] who had CLS-D)			
Once	95 (30.6%)	1 (7.7%)	14 (26.9%)
2–10 times	155 (50.0%)	11 (84.6%)	26 (50.0%)
≥11 times	60 (19.4%)	1 (7.7%)	12 (23.1%)
Number of times not given	16	10	15
Type CLS-D partner(s), (*N* = 408[f] who had CLS-D)			
Long-term partner only	76 (23.9%)	18 (78.3%)	63 (94.0%)
Long-term partner and other partner(s)	19 (6.0%)	–	–
Other partner(s)	223 (70.1%)	5 (21.7%)	4 (6.0%)
Missing partner type	8	–	–
Type CLS-D sex (for MSM only), (*N* = 314 MSM[g] who had CLS-D)			
CLS-D anal sex with men			
Insertive anal sex with ejaculation	88 (28.0%)		
Insertive anal sex without ejaculation	92 (29.3%)		
Receptive anal sex	126 (40.1%)		
CLS-D with women only	8 (2.5%)		
CLS-D anal sex with men, missing type	12		
Sexually transmitted infection diagnosed in past 3 months, (*N* = 3178)	235 (10.7%)	16 (4.4%)	35 (5.6%)
Had group sex[h] in past 3 months, (*N* = 3178)	453 (20.7%)	2 (0.6%)	5 (0.8%)
≥10 new sexual partners in past year, (*N* = 2913)	533 (25.9%)	0 (0%)	1 (0.2%)
Believe that HIV transmission risk very low indicated as reason for not using condom on last occasion of CLS-D, (*N* = 416 who had CLS-D)	122 (37.4%)	8 (34.8%)	27 (40.3%)
Transmission risk belief score[j], (*N* = 3129)			
2: If viral load undetectable, condom not needed to prevent HIV transmission	99 (4.6%)	35 (10.0%)	47 (7.7%)
1: Less infectious if viral load undetectable (but does not agree with 2 above)	1023 (47.3%)	122 (34.8%)	233 (38.0%)
0: Does not agree with either of 1 or 2 above	1043 (48.2%)	194 (55.3%)	333 (54.3%)

[a]All variables relate to a 3-month recall period unless otherwise indicated.
[b]Includes those who reported CLS, but did not specify whether with HIV serodifferent or concordant status partner(s).
[c]Of all those reporting anal/vaginal sex; percentages are given of 1329, 214 and 284 non-missing values for MSM, heterosexual men, women.
[d]Of all those reporting CLS-D; percentages are given of 313 non-missing values for MSM.
[e]Of all those reporting CLS-D; percentages are given of 310, 13 and 52 all non-missing values for MSM, heterosexual men, women.
[f]Of all those reporting CLS-D; percentages are given of 318 non-missing values for MSM.
[g]Of all those reporting CLS-D; percentages are given of 314 non-missing values for MSM.
[h]Sex with more than one person on the same occasion.
[i]20 had sex with both men and women, and 12 had sex with women only.
[j]Hierarchical classification.

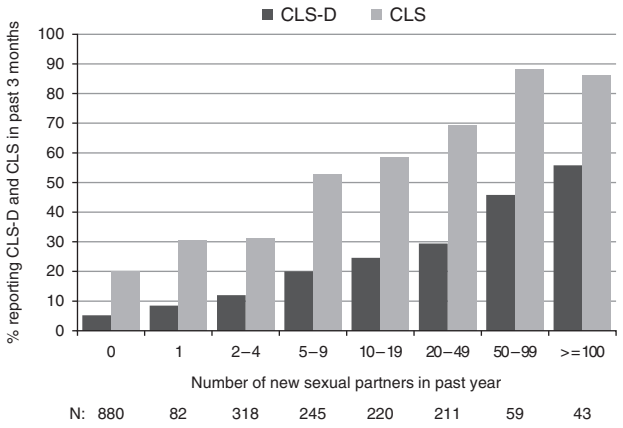

Fig. 1. Prevalence of condomless sex (CLS) and condomless sex with HIV-serodifferent partner (CLS-D) in the past three months according to number of new sexual partners reported in the past year, among MSM diagnosed with HIV more than 3 months ago. *N*, 2058 MSM with information on number of new sexual partners in past year. Among 131 MSM with missing data on new sexual partners, prevalence of CLS-D and CLS was 14.5 and 31.3%, respectively.

CLS-D was usually with a long-term partner, recent STI was less common and prevalence of group sex and multiple partners was very low.

Among 351 heterosexual men with information on self-reported ART/viral load, there were no significant differences between those on ART vs. not on ART in prevalence of vaginal/anal sex (63.6% vs. 70.8%), CLS (23.9% vs. 16.7%) and CSL-D (6.4% vs. 4.2%) in the past 3 months. Similarly, among 611 women, ART was not associated with vaginal/anal sex (50.6% vs. 54.4% for on versus not on ART), CLS (21.4% vs. 23.5%) or CLS-D (11.2% vs. 8.8%) ($P > 0.3$ for all, χ^2/Fisher's exact test). Table 3b shows associations for all heterosexual participants combined. Self-reported ART/viral load was not associated with CLS-D. CLS-D was associated with younger age, birth in the United Kingdom, non-black ethnicity, university education, not having a recent HIV diagnosis, higher CD4+ cell count and tended to be associated with greater financial security. CLS-D prevalence was much lower among the majority of individuals who identified with a religion than the minority who did not, and much higher among people with an HIV-negative/unknown status stable partner. CLS-D was associated with recreational drug use, but not with smoking or alcohol use. Patterns of association were broadly similar with all CLS. There remained no significant association of self-reported ART/viral load with CLS-D among heterosexual individuals in adjusted models (Table 4b).

Transmission risk beliefs

Table 2 shows that the vast majority of participants believed in the need for condoms, even with undetectable viral load, and approximately half did not agree that undetectable viral load reduced infectiousness. However, of all 416 participants who reported CLS-D, just over a third (37.7%) gave 'belief that transmission risk is very low' as one reason for not using a condom. This percentage was 41.9% among participants on ART with undetectable self-reported viral load, compared with 23.1% among those on ART without undetectable self-reported viral load, and 27.9% among those not on ART ($P = 0.008$, χ^2).

Self-reported antiretroviral treatment/viral load and HIV-transmission risk sex

Among 2142 participants on ART who reported undetectable viral load, the vast majority (96.5%; $n = 2066$) had clinic-recorded viral load 50 copies/ml or less. Conversely, of all 2389 with clinic viral load 50 copies/ml or less, 86.5% had undetectable self-reported viral load. Prevalence of CLS-D-HIV-risk (CLS-D together with either 'not on ART' or clinic-recorded viral load >50 copies/ml) was 3.2% (101/3178) overall, 16.1% (61/379) among those not on ART (by definition equivalent to CLS-D), 0.6% (14/2154) among those on ART with undetectable self-reported viral load (the 14 cases because of CLS-D together with clinic viral load >50 copies/ml despite undetectable self-reported viral load), and 4.2% (25/592) among those on ART without undetectable self-reported viral load. Among MSM, these proportions were 3.9% (85/2189) overall, and 18.8% (54/287), 0.8% (12/1569) and 5.9% (18/307) respectively for the three self-reported ART/viral load categories. Among heterosexual individuals, corresponding proportions were 1.6% (16/989) overall; 7.6% (7/92), 0.3% (2/585) and 2.5% (7/285) for the self-reported ART/viral load categories. Therefore, prevalence of CLS-D-HIV-risk was much lower among people on ART, and extremely low (<1%) among those on ART with undetectable self-reported viral load.

Sensitivity analyses

Among MSM, when defining CLS-D to include possible CLS-D, adjusted prevalence ratios (95% CI) from model 2 were: 0.74 (0.53, 1.04) for 'ART without undetectable self-reported viral load' and 1.06 (0.78, 1.44) for 'not on ART', compared with 'ART with undetectable self-reported viral load' (global $P = 0.11$). Including only MSM who had sex in the past 3 months, corresponding adjusted prevalence ratios (95% CI) were 0.68 (0.48, 0.96) and 0.98 (0.72, 1.33) ($P = 0.042$). Among MSM diagnosed less than 5 years ago, adjusted prevalence ratios (95% CI) were 0.22 (0.08, 0.59) for 'ART without undetectable self-reported viral load', and 0.70 (0.46, 1.07) for 'not on ART', compared with 'ART with undetectable self-reported viral load'. Among MSM diagnosed 5 years ago or more, corresponding adjusted prevalence ratios (95% CI) were 0.88 (0.59, 1.31) and 1.60 (1.10, 2.33); this interaction was significant ($P = 0.001$). Among heterosexual individuals, there was no significant association between self-reported

Table 3. Condomless sex with HIV-serodifferent partner (CLS-D), and all condomless sex (CLS), in the past three months, according to self-reported ART/viral load status and other factors, among 3178 individuals diagnosed with HIV more than 3 months ago: (a) 2189 MSM and (b) 989 heterosexual men and women.

	(a) MSM ($N=2189$)			(b) Heterosexual men and women ($N=989$)		
	N	n (%) CLS-D	n (%) CLS	N	n (%) CLS-D	n (%) CLS
Self-reported ART status (1)						
Not on ART	287	54 (18.8)	139 (48.4)	92	7 (7.6)	20 (21.7)
On ART	1876	268 (14.3)	692 (36.9)	870	82 (9.4)	194 (22.3)
		$P=0.045$	$P<0.001$		$P=0.57$	$P=0.90$
Self-reported ART status (2)						
Never taken ART	253	42 (16.6)	123 (48.6)	61	6 (9.8)	16 (26.2)
Ever taken ART	1910	280 (14.7)	708 (37.1)	901	83 (9.2)	198 (22.0)
		$P=0.42$	$P<0.001$		$P=0.87$	$P=0.44$
Self-reported ART status (3)						
Never taken ART	253	42 (16.6)	123 (48.6)	61	6 (9.8)	16 (26.2)
Stopped ART	34	12 (35.3)	16 (47.1)	31	1 (3.2)	4 (12.9)
On ART	1876	268 (14.3)	692 (36.9)	870	82 (9.4)	194 (22.3)
		$P=0.002$	$P<0.001$		$P=0.50$	$P=0.35$
Self-reported ART and viral load status						
Not on ART	287	54 (18.8)	139 (48.4)	92	7 (7.6)	20 (21.7)
On ART, viral load$\leq$50 copies/ml	1569	238 (15.2)	594 (37.9)	585	60 (10.3)	137 (23.4)
On ART, viral load>50 copies/ml or unknown[a]	307	30 (9.8)	98 (31.9)	285	22 (7.7)	57 (20.0)
		$P=0.007$	$P<0.001$		$P=0.41$	$P=0.52$
Age group (years)						
<30	96	23 (24.0)	56 (58.3)	63	8 (12.7)	15 (23.8)
30–39	487	75 (15.4)	233 (47.8)	233	27 (11.6)	57 (24.5)
40–49	929	144 (15.5)	354 (38.1)	415	33 (8.0)	94 (22.7)
50–59	503	62 (12.3)	154 (30.6)	174	18 (10.3)	36 (20.7)
$\geq$60	152	18 (11.8)	33 (21.7)	60	1 (1.7)	4 (6.7)
		$P=0.008^{\#}$	$P<0.001^{\#}$		$P=0.049^{\#}$	$P=0.020^{\#}$
Ethnicity						
White	1931	282 (14.6)	739 (38.3)	236	29 (12.3)	65 (27.5)
Black African	21	3 (14.3)	4 (19.1)	580	46 (7.9)	123 (21.2)
Black other	54	8 (14.8)	23 (42.6)	69	3 (4.3)	9 (13.0)
Other/missing	183	33 (18.0)	70 (38.3)	104	12 (11.5)	19 (18.3)
		$P=0.67$	$P=0.29$		$P=0.090$	$P=0.036$
UK birth						
Yes	1532	226 (14.8)	583 (38.1)	208	27 (13.0)	61 (29.3)
No	629	96 (15.3)	244 (38.8)	736	58 (7.9)	146 (19.8)
		$P=0.76$	$P=0.75$		$P=0.023$	$P=0.004$
Education						
University	954	149 (15.6)	391 (41.0)	324	38 (11.7)	87 (26.9)
Other/missing	1235	177 (14.3)	445 (36.0)	665	52 (7.8)	129 (19.4)
		$P=0.40$	$P=0.018$		$P=0.045$	$P=0.008$
Employment status						
Employed (full or part time)	1326	211 (15.9)	562 (42.4)	440	49 (11.1)	119 (27.1)
Unemployed	309	46 (14.9)	109 (35.3)	254	19 (7.5)	53 (20.9)
Not working: sick or disabled	316	42 (13.3)	104 (32.9)	100	7 (7.0)	11 (11.0)
Other (student, looking after home, retired, other)	203	22 (10.8)	51 (25.1)	149	11 (7.4)	26 (17.4)
		$P=0.23$	$P<0.001$		$P=0.25$	$P=0.002$
Money for basic needs?						
Always	1116	164 (14.7)	431 (38.6)	230	26 (11.3)	57 (24.8)
Mostly	597	85 (14.2)	223 (37.4)	226	25 (11.1)	53 (23.5)
Sometimes	277	40 (14.4)	108 (39.0)	279	17 (6.1)	61 (21.9)
No	173	32 (18.5)	65 (37.6)	218	18 (8.3)	37 (17.0)
		$P=0.40^{\#}$	$P=0.83^{\#}$		$P=0.082^{\#}$	$P=0.045^{\#}$
Identify with a religion?						
Yes	934	144 (15.4)	342 (36.6)	833	61 (7.3)	163 (19.6)
No/missing	1255	182 (14.5)	494 (39.4)	156	29 (18.6)	53 (34.0)
		$P=0.55$	$P=0.19$		$P<0.001$	$P<0.001$
Time since HIV diagnosis						
3 months to 1.9 years	184	29 (15.8)	72 (39.1)	109	4 (3.7)	18 (16.5)
2–4.9 years	338	57 (16.9)	157 (46.5)	160	17 (10.6)	36 (22.5)
5–9.9 years	550	96 (17.5)	240 (43.6)	343	33 (9.6)	80 (23.3)
10–14.9 years	461	69 (15.0)	168 (36.4)	186	16 (8.6)	37 (19.9)
15–19.9 years	376	47 (12.5)	126 (33.5)	112	11 (9.8)	25 (22.3)
$\geq$20 years	268	26 (9.7)	69 (25.7)	63	9 (14.3)	17 (27.0)
		$P=0.005^{\#}$	$P<0.001^{\#}$		$P=0.11^{\#}$	$P=0.31^{\#}$
					$P=0.033^{d}$	$P=0.15^{d}$

Table 3 (*continued*)

	(a) MSM ($N=2189$)			(b) Heterosexual men and women ($N=989$)		
	N	*n* (%) CLS-D	*n* (%) CLS	*N*	*n* (%) CLS-D	*n* (%) CLS
Partner status						
HIV+ stable partner	512	47 (9.2)	309 (60.4)	234	2 (0.9)	106 (45.3)
HIV- or HIV-unknown status stable partner	674	141 (20.9)	198 (29.4)	353	78 (22.1)	95 (26.9)
No stable partner	987	136 (13.8)	326 (33.0)	394	10 (2.5)	15 (3.8)
		$P<0.001$	$P<0.001$		$P<0.001$	$P<0.001$
Current smoker						
No/missing	1377	218 (15.8)	506 (36.8)	814	73 (9.0)	172 (21.1)
Yes	812	108 (13.3)	330 (40.8)	175	17 (9.7)	44 (25.1)
		$P=0.11$	$P=0.070$		$P=0.76$	$P=0.24$
Higher alcohol consumption[b]						
No/missing	1821	251 (13.8)	684 (37.7)	933	86 (9.2)	201 (21.5)
Yes	368	75 (20.4)	152 (41.6)	56	4 (7.1)	15 (26.8)
		$P=0.001$	$P=0.18$		$P=0.60$	$P=0.36$
Number of recreational drugs used in past 3 months						
None/missing	1078	103 (9.6)	259 (24.0)	888	73 (8.2)	183 (20.6)
1	364	51 (14.0)	119 (32.7)	72	13 (18.1)	26 (36.1)
2–3	403	84 (20.8)	204 (50.6)	28	4 (14.3)	7 (25.0)
≥4	344	88 (25.6)	254 (73.8)	1	0 (0)	0 (0)
		$P<0.001^{\#}$	$P<0.001^{\#}$		$P=0.004$[d]	$P=0.005$[d]
Clinic-recorded $CD4^+$ cell count (cells/μl)[c]						
<200	77	11 (14.3)	21 (27.3)	72	1 (1.4)	9 (12.5)
200–349	240	32 (13.3)	80 (33.3)	166	12 (7.2)	32 (19.3)
250–499	538	79 (14.7)	215 (40.0)	234	19 (8.1)	51 (21.8)
≥500	1320	201 (15.2)	516 (39.1)	508	57 (11.2)	121 (23.8)
		$P=0.49^{\#}$	$P=0.033^{\#}$		$P=0.004^{\#}$	$P=0.026^{\#}$
Clinic-recorded viral load (copies/ml)[c]						
≤50	1694	243 (14.3)	617 (36.4)	767	77 (10.0)	173 (22.6)
>50	481	82 (17.1)	217 (45.1)	215	13 (6.1)	42 (19.5)
		$P=0.14$	$P<0.001$		$P=0.073$	$P=0.34$

Denominators vary because of missing values. Self-reported ART status missing for 53 participants (26 MSM, nine heterosexual men and 18 women). Prevalence of CLS-D and CLS among participants with missing current ART status: 15.4 and 19.2% for 26 MSM; 3.7 and 7.4% for 27 heterosexual men and women. Univariate *P* values by χ^2 tests.

[#] χ^2 tests for trend.

[a] Includes 'do not know' viral load level and missing response.

[b] Score of 6 or more on modified WHO AUDIT C questionnaire (using first two questions only).

[c] Latest clinic-recorded value that participant had been informed of.

[d] Among heterosexuals, for time with diagnosed HIV, *P* value corresponds to comparison of '3 months to 1.9 years' with '2 years or more', using χ^2 test. For recreational drug use, *P* value corresponds to comparison of 'no drug use' with 'drug use', using χ^2 test.

ART/viral load and CLS-D for sensitivity analyses a–c (data not shown).

Discussion

In this large multicentre study of people attending HIV clinics in the United Kingdom in 2011/12, use of ART was not associated with higher prevalence of CLS-D. Among MSM, those on ART had moderately *lower* prevalence of CLS-D than those not on ART, although this association was not independent of time since HIV diagnosis. Among MSM on ART, those who reported undetectable viral load had higher levels of CLS-D than those who did not, but CLS-D prevalence in both 'on ART' groups was lower than for MSM not on ART. Among heterosexual men and women, self-reported ART/viral load was not significantly associated with CLS-D. Patterns were similar for CLS overall. The prevalence of CLS-D-HIV-risk was low in the study population overall, and extremely low among those on ART with undetectable self-reported viral load.

With few exceptions [18,21,23], previous epidemiological studies [19,20,22–26,28–33] have found either no association of CLS-D with ART use and/or suppressed viral load, or that people on ART had somewhat lower levels of CLS-D. Similarly, a randomized comparison within the SMART trial (2002–2006) found that starting ART led to a reduction in CLS-D in the short term [27]. The most recent observational study used data from 2009, a few years prior to ASTRA. Interview-assessed sexual behaviour was linked to recorded viral load among a large sample of United States' HIV outpatients (Medical Monitoring Project) [33]. Self-reported viral load was not assessed. Similar to ASTRA results comparing 'on ART' with 'not on ART', the United States' study found

Table 4. Unadjusted and adjusted associations of self-reported ART/viral load status with condomless sex with HIV-serodifferent partner (CLS-D), in the past three months, among 3178 individuals diagnosed with HIV more than 3 months ago: (a) 2189 MSM and (b) 989 heterosexual men and women.

	(a) MSM ($N=2198$)			(b) Heterosexual men and women ($N=989$)		
	Unadjusted prevalence ratio (95% CI)	Adjusted (1)[b] prevalence ratio (95% CI)	Adjusted (2)[c] prevalence ratio (95% CI)	Unadjusted prevalence ratio (95% CI)	Adjusted (1)[b] prevalence ratio (95% CI)	Adjusted (2)[c] prevalence ratio (95% CI)
Associations with CLS-D	$N=2189$[d]	$N=2118$	$N=2118$	$N=989$[d]	$N=908$	$N=908$
Gender						
Male				1	1	1
Female				1.67 (1.06, 2.63) $P=0.017$	2.02 (1.29, 3.17) $P<0.001$	2.11 (1.34, 3.33) $P<0.001$
Self-reported ART/viral load status						
Not on ART	1.24 (0.95, 1.62)	1.08 (0.78, 1.49)	1.01 (0.74, 1.39)	0.74 (0.35, 1.57)	0.88 (0.44, 1.77)	0.87 (0.43, 1.77)
On ART, viral load ≤ 50 copies/ml	1	1	1	1	1	1
On ART, viral load >50 copies/ml or unknown[e]	0.64 (0.45, 0.92) $P=0.003$	0.66 (0.45, 0.95) $P=0.021$	0.64 (0.44, 0.92) $P=0.015$	0.75 (0.47, 1.20) $P=0.39$	1.14 (0.73, 1.79) $P=0.77$	1.20 (0.76, 1.87) $P=0.67$
Age						
<30 years	1	1	1	1	1	1
≥30 years	0.60 (0.42, 0.87) $P=0.035$	0.64 (0.43, 0.95) $P=0.062$	0.76 (0.51, 1.13) $P=0.21$	0.71 (0.36, 1.39) $P=0.39$	1.14 (0.61, 2.11) $P=0.67$	1.29 (0.70, 2.38) $P=0.38$
Black ethnicity						
No/missing	1	1	1	1	1	1
Yes	0.98 (0.56, 1.72) $P=0.96$	0.95 (0.53, 1.69) $P=0.86$	0.97 (0.56, 1.68) $P=0.92$	0.63 (0.42, 0.93) $P=0.028$	0.94 (0.60, 1.46) $P=0.76$	0.98 (0.63, 1.51) $P=0.92$
University education						
No/missing	1	1	1	1	1	1
Yes	1.09 (0.89, 1.33) $P=0.40$	1.04 (0.85, 1.28) $P=0.71$	1.04 (0.85, 1.27) $P=0.71$	1.50 (1.01, 2.23) $P=0.060$	1.12 (0.77, 1.64) $P=0.55$	1.21 (0.83, 1.77) $P=0.33$
Identifies with a religion						
No/missing	1	1	1	1	1	1
Yes	1.06 (0.87, 1.30) $P=0.55$	1.09 (0.89, 1.34) $P=0.40$	1.22 (1.00, 1.49) $P=0.056$	0.39 (0.26, 0.59) $P<0.001$	0.41 (0.26, 0.65) $P<0.001$	0.47 (0.30, 0.73) $P=0.002$
Time with diagnosed HIV						
3 months to 1.9 years	1	1	1	1	1	1
2–4.9 years	1.07 (0.71, 1.61)	1.12 (0.74, 1.70)	1.12 (0.75, 1.69)	2.71 (1.02, 7.25)[g]	2.16 (0.88, 5.30)[g]	2.16 (0.91, 5.15)[g]
5–9.9 years	1.11 (0.70, 1.62)	1.18 (0.77, 1.79)	1.23 (0.82, 1.85)			
10–14.9 years	0.95 (0.64, 1.41)	1.06 (0.68, 1.65)	1.11 (0.72, 1.71)			
15–19.9 years	0.79 (0.52, 1.22)	0.84 (0.52, 1.35)	0.86 (0.54, 1.37)			
≥20 years	0.62 (0.38, 1.01) $P=0.003$[a]	0.71 (0.42, 1.21) $P=0.025$[a]	0.81 (0.48, 1.35) $P=0.071$[a]	$P=0.003$	$P=0.028$	$P=0.021$
Partner status						
HIV+ stable partner	1	1	1	1	1	1
HIV- or HIV-unknown stable partner	2.28 (1.67, 3.11)	2.34 (1.71, 3.19)	2.63 (1.93, 3.57)	25.8 (6.4, 104.2)	22.7 (5.6, 91.5)	22.3 (5.50, 90.0)
No stable partner	1.50 (1.10, 2.05) $P<0.001$	1.54 (1.12, 2.12) $P<0.001$	1.63 (1.19, 2.24) $P<0.001$	2.97 (0.66, 13.4) $P<0.001$	2.51 (0.54, 11.6) $P<0.001$	2.42 (0.53, 11.1) $P<0.001$
Higher alcohol consumption[f]						
No/missing	1		1	1		1
Yes	1.48 (1.17, 1.87) $P=0.004$		1.34 (1.06, 1.68) $P=0.022$	0.77 (0.30, 2.04) $P=0.56$		0.74 (0.25, 2.14) $P=0.52$

Table 4 (*continued*)

Associations with CLS-D	(a) MSM ($N=2198$) Unadjusted prevalence ratio (95% CI)	Adjusted (1)[b] prevalence ratio (95% CI)	Adjusted (2)[c] prevalence ratio (95% CI)	(b) Heterosexual men and women ($N=989$) Unadjusted prevalence ratio (95% CI)	Adjusted (1)[b] prevalence ratio (95% CI)	Adjusted (2)[c] prevalence ratio (95% CI)
	$N=2189$[d]	$N=2118$	$N=2118$	$N=989$[d]	$N=908$	$N=908$
Number of recreational drugs used in past 3 months						
None/missing	1		1	1		1
1	1.48 (1.07, 2.01)		1.40 (1.07, 2.03)	2.05 (1.26, 3.33)[g]		1.96 (1.25, 3.07)[g]
2–3	2.18 (1.67, 2.84)		2.18 (1.67, 2.85)			
≥4	2.83 (2.07, 3.46)		2.82 (2.17, 3.69)			
	$P<0.001$[a]		$P<0.001$[a]	$P=0.028$		$P=0.014$

Prevalence ratios from modified Poisson regression model with robust error variances. P values by score statistic.
[a]Test for trend.
[b]Adjusted 1: model includes self-reported ART/viral load; age; ethnicity; education; religion; time with diagnosed HIV; partner status, together with gender for heterosexual model.
[c]Adjusted 2: model includes all factors in model 1 plus alcohol consumption and recreational drugs use.
[d]Denominators vary because of missing values, see Table 1.
[e]Includes 'do not know' viral load level and missing response.
[f]Score of 6 or more on modified WHO AUDIT C questionnaire (using first two questions only).
[g]Heterosexual models: for time with diagnosed HIV '2 years or more' is compared with '3 months to 1.9 years', for recreational drug use, 'drug use' is compared with 'no drug use'.

that individuals with viral load suppression had lower levels of sex, CLS, and CLS-D than those without; the association was significant only for MSM.

For MSM on ART in ASTRA, the prevalence of CLS-D was higher among those who reported undetectable viral load than among those who did not. This modest difference remained after adjustment for other factors, and among the subgroup of MSM who had recent sex (sensitivity analysis b), therefore was not due to those on ART being less likely to be sexually active. The difference was particularly marked among those more recently diagnosed (sensitivity analysis c). Although there may be other differences between the two 'on ART' groups, one plausible explanation is that some MSM were choosing not to use a condom with HIV-serodifferent partners because of knowledge of very low infectiousness based on their perceived viral load. Consistent with this, of all participants who reported CLS-D, belief that transmission risk was low was more frequently a reason for not using condoms among those with undetectable self-reported viral load than those without. However, if knowledge of viral load was influencing sexual behaviour among MSM, the effect appeared modest, because levels of CLS-D among those on ART with undetectable self-reported viral load did not exceed those for men not on ART.

Prevalence estimates of CLS-D among MSM (15%) and heterosexual men (6%) and women (11%) with HIV in ASTRA are similar to those from two clinic-based studies in the United Kingdom in 2004–2005 using an identical definition (20 and 15% among 758 [22] and 451 [29] MSM, respectively; less than 10% among heterosexual men and women [22,29]), and from the European START trial participants at baseline: 15, 3 and 10% in the past 2 months for 1518 MSM, 207 heterosexual men and 138 women with HIV not taking ART (recently diagnosed participants were included) [41]. The START analysis found no significant trend in baseline CLS-D prevalence over the recruitment period (2009–2013). Taken together these results suggest levels of CLS-D among people with HIV have remained fairly stable in the past decade, emphasising further that any change related to new messages about 'safe sex' has not been significant. Comparison with other studies is complicated by different recall periods and sampling frames: internet and venue-based studies tend to yield higher CLS-D estimates among HIV-positive MSM [42,43], which may be because of selection bias. Consistent with other studies [41,44–46], ASTRA suggests that perceived risk-reduction strategies (withdrawal before ejaculation and being the receptive partner) are commonly used among HIV-positive MSM having CLS-D.

Among MSM in ASTRA, CLS-D prevalence was lower with longer time since diagnosis, and higher among younger men, those without an HIV-positive stable partner, and those with higher alcohol and drug use, but

CLS-D was not linked to socio-economic status. Similarly, among MSM in START, CLS-D was not associated with education level [41]. We have previously described the strong link between polydrug use and CLS/CLS-D among MSM [40], in part reflecting use of 'chemsex' [47]. Among heterosexual individuals in ASTRA, factors associated with CLS-D included white ethnicity, and higher socio-economic status in unadjusted analysis. In contrast, among heterosexual individuals in START, CLS-D tended to be associated with non-white ethnicity and lower education in unadjusted analysis [41]. START had a diverse international population; socio-demographic effects on sexual behaviour may vary across cultural settings. Among heterosexuals in ASTRA, female sex, not having a recent HIV diagnosis, not identifying with a religion and recreational drug use were independent correlates of CLS-D, but the dominant association was with having an HIV-negative stable partner – this was the context of CLS-D for most heterosexual men and women who reported it. There may be specific issues relating to CLS-D in this context, such as desire for conception, or mutuality of decision making about condom use.

ASTRA is the largest questionnaire study of sexual behaviour among people living with HIV in the United Kingdom; although power to assess associations among heterosexual men and women separately was limited. Participants were reassured that questionnaire responses were confidential and would not be seen by clinic staff. Nevertheless, self-reported behaviour and attitudes may be subject to errors and social desirability bias.

What are the implications of these results for HIV-transmission? The prevalence of 'HIV-transmission risk sex' was much lower among those on ART vs. not on ART (1.4% vs 16.1%), and less than 1% among those on ART with undetectable self-reported viral load. Even if the ASTRA results do indicate the start of a trend of increasingly higher levels of CLS-D with perceived undetectable viral load (among MSM or the HIV-diagnosed population overall), prevalence of CLS-D-HIV-risk will likely continue to remain far lower among those on ART with undetectable self-reported viral load than among those not on ART. This is because of the effectiveness of ART and the apparent high accuracy of self-reported undetectable viral load status in this population. These results highlight the importance, as ART use expands, of promoting sustained high adherence, regular viral load testing, and on-going awareness of personal viral load level. It is also important to note that the definition of CLS-D-HIV-risk used here is based on the single clinic viral load measurement collected for all ASTRA participants, assumes elimination of risk with viral suppression on ART (as assumed with condom use), and does not incorporate factors such as self-reported ART non-adherence or presence of other STIs, the additional impact of which are uncertain [13,48].

In terms of transmission of other STIs, CLS overall is the most relevant measure. Similar to CLS-D, CLS prevalence among MSM was highest for those not on ART with no significant difference by ART use among heterosexual individuals. Therefore these data give little suggestion that expansion of ART use will have a negative impact on STI transmission. Nevertheless, the high prevalence of CLS compared with CLS-D-HIV risk, and the possibility that levels of CLS among those with undetectable self-reported viral load may continue to increase, emphasise the importance of ongoing promotion of condom use, STI prevention and testing among people with HIV.

The ASTRA study was planned in the period following the Swiss statement, which was then hugely controversial [49]. During recruitment, results were released from HPTN 052 [12]; PARTNER results were first presented after completion of ASTRA [13]. During this period United Kingdom [37] and other [50,51] treatment guidelines were changed to recommend discussing with HIV-positive people the beneficial effect of ART on infectiousness. The extent to which, and the rapidity with which, these findings and recommendations may influence the sexual behaviour of people with HIV [52], or change the long-standing culture of condom use [3], is unclear. With increasing use of early ART, it will be important to continue monitoring the association between ART and CLS, not only to understand the impact on HIV transmission, but also to assess implications for transmission of hepatitis C and other STIs.

In conclusion, among people with HIV in the United Kingdom, use of ART was not associated with increased prevalence of CLS or CLS-D, and was associated with greatly reduced prevalence of HIV-transmission risk sex. Although there was evidence that perceived undetectable viral load may influence condom use among MSM, any such effect was modest at the time of the study, and would not undermine the effect of early ART on HIV/STI transmission. These results support the prevention role of ART offered to all people with HIV, and emphasise the need to focus on HIV/STI prevention among those not on ART.

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Conflicts of interest

The authors declare the following conflicts of interest: AP - consultancy with GSK Biologicals; advisory board for Abbvie, Gilead Sciences; speaker's fees (Gilead Sciences). EW- travel bursaries, honoraria for lectures and advisory boards from Gilead, Janssen, Merck-Sharpe-Dohme, Bristol-Myers-Squibb, AbbVie, Abbott, and ViiV over the last 24 months. JA - grants and personal fees from Gilead Sciences, personal fees from ViiV, MSD, Bristol Myers Squibb, Jansen, Abbvie, outside the submitted work. AMG - consultancy and speaker's fees from Abbvie, Bristol Meyers Squibb (BMS), Gilead, GlaxoSmithKline (GSK), Janssen, Pfizer, and ViiV; the University of Liverpool receives grant funding from BMS, Gilead, Janssen and ViiV for research studies of which AMG is the principal investigator, and fees from Abbott Molecular and Pfizer for consultancy work provided by AMG. FCL, MD, AS, MAJ, RG, RO, ML, KA, JM, JE, SC, SE, NP, LS, GH, AMJ, AM, WJB, AJR declared no conflicts of interest.

References

1. Yin Z, Brown A, Hughes G, Nardone A, Gill ON, Delpech VC, *et al*. **HIV in the United Kingdom 2014 Report: data to end 2013.** November 2014. London: Public Health England.

2. Birrell PJ, Gill ON, Delpech VC, Brown AE, Desai S, Chadborn TR, *et al*. **HIV incidence in men who have sex with men in England and Wales 2001-10: a nationwide population study.** *Lancet Infect Dis* 2013; **13**:313–318.
3. Phillips AN, Cambiano V, Nakagawa F, Brown AE, Lampe F, Rodger A, *et al*. **Increased HIV incidence in men who have sex with men despite high levels of ART-induced viral suppression: analysis of an extensively documented epidemic.** *PLoS One* 2013; **8**:e55312.
4. Brown AE, Gill ON, Delpech VC. **HIV treatment as prevention among men who have sex with men in the UK: is transmission controlled by universal access to HIV treatment and care?** *HIV Med* 2013; **14**:563–570.
5. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. **Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.** *Lancet* 2009; **373**:48–57.
6. US Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2012. http://aidsinfo.nih.gov/guidelines.
7. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, *et al*. **Viral load and heterosexual transmission of human immunodeficiency virus type 1.** *N Engl J Med* 2000; **342**:921–929.
8. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, *et al*. **Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa.** *AIDS Res Hum Retroviruses* 2001; **17**:901–910.
9. Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, *et al*. **Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand.** *J Acquir Immune Defic Syndr* 2002; **29**:275–283.
10. Attia S, Egger M, Müller M, Zwahlen M, Low N. **Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis.** *AIDS* 2009; **23**:1397–1404.
11. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, *et al*. **Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis.** *Lancet* 2010; **375**:2092–2098.
12. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, *et al*. **Prevention of HIV-1 infection with early antiretroviral therapy.** *N Engl J Med* 2011; **365**:493–505.
13. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Van Lunzen J, *et al*. **Association between sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy: The PARTNER STUDY.** *JAMA* in press.
14. The INSIGHT START Study Group. **Initiation of antiretroviral therapy in early asymptomatic HIV infection.** *New Engl J Med* 2015; **373**:795–807.
15. World Health Organization. Guideline on when to start antiretroviral therapy and on preexposure prophylaxis for HIV. 2015. http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/ [Accessed March 2016].
16. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy. 2015. http://www.bhiva.org/HIV-1-treatment-guidelines.aspx [Accessed March 2016].
17. Vernazza P, Hirschel B, Bernasconi E, Flepp M. **Les personnes séropositives ne souffrant d'aucune autre MST et suivant un traitment antirétroviral efficace ne transmettent pas le VIH par voie sexuelle.** *Bull des Médecins Suisses* 2008; **89**:165–169.
18. Hasse B, Ledergerber B, Hirschel B, Vernazza P, Glass TR, Jeannin A, *et al*. **Frequency and determinants of unprotected sex among HIV-infected persons: the Swiss HIV cohort study.** *Clin Infect Dis* 2010; **51**:1314–1322.
19. Crepaz N, Hart TA, Marks G. **Highly active antiretroviral therapy and sexual risk behaviour: a meta-analytic review.** *JAMA* 2004; **292**:224–236.
20. Kozal MJ, Amico KR, Chiarella J, Schreibman T, Cornman D, Fisher W, *et al*. **Antiretroviral resistance and high-risk transmission behavior among HIV-positive patients in clinical care.** *AIDS* 2004; **18**:2185–2189.
21. Van de Ven P, Mao L, Fogarty A, Rawstorne P, Crawford J, Prestage G, *et al*. **Undetectable viral load is associated with sexual risk taking in HIV serodiscordant gay couples in Sydney.** *AIDS* 2005; **19**:179–184.
22. Elford J, Ibrahim F, Bukutu C, Anderson J. **Sexual behaviour of people living with HIV in London: implications for HIV transmission.** *AIDS* 2007; **21 (Suppl 1)**:S63–S70.
23. Seng R, Rolland M, Beck-Wirth G, Souala F, Deveau C, Delfraissy JF, *et al*. **Trends in unsafe sex and influence of viral load among patients followed since primary HIV-infection, 2000–2009.** *AIDS* 2011; **25**:977–988.
24. Stephenson JM, Imrie J, Davis MM, Mercer C, Black S, Copas AJ, *et al*. **Is use of antiretroviral therapy among homosexual men associated with increased risk of transmission of HIV infection?** *Sex Transm Infect* 2003; **79**:7–10.
25. Glass TR, Young J, Vernazza PL, Rickenbach M, Weber R, Cavassini M, *et al*. **Is unsafe sexual behaviour increasing among HIV-infected individuals?** *AIDS* 2004; **18**:1707–1714.
26. Morin SF, Myers JJ, Shade SB, Koester K, Maiorana A, Dawson Rose C. **Predicting HIV transmission risk among HIV-infected patients seen in clinical settings.** *AIDS Behav* 2007; **11 (Suppl 5)**:S6–S16.
27. Burman W, Grund B, Neuhaus J, Douglas J Jr, Friedland G, Telzak E, *et al*. **Episodic antiretroviral therapy increases HIV transmission risk compared with continuous therapy: results of a randomized controlled trial.** *J Acquir Immune Defic Syndr* 2008; **49**:142–150.
28. Golin C, Marks G, Wright J, Gerovich M, Tien H, Patel SN, *et al*. **Psychosocial characteristics and sexual behaviours of people in care for HIV infection: an examination of men who have sex with men, heterosexual men and women.** *AIDS Behav* 2009; **13**:1129–1142.
29. Harding R, Clucas C, Lampe FC, Norwood S, Leake-Date H, Fisher M, *et al*. **Behavioural surveillance study: sexual risk taking behaviour in UK HIV outpatient attendees.** *AIDS Behav* 2012; **16**:1708–1715.
30. Kalichman SC, Cherry C, White D, Jones M, Grebler T, Kalichman MO, *et al*. **Sexual HIV transmission and antiretroviral therapy: a prospective cohort study of behavioural risk factors among men and women living with HIV/AIDS.** *Ann Behav Med* 2011; **42**:111–119.
31. Cunha CB, De Boni RB, Guimaraes MRC, Yanavich C, Veloso VC, Moreira RI, *et al*. **Unprotected sex among men who have sex with me living with HIV in Brazil: a cross-sectional study in Rio de Janeiro.** *BMC Public Health* 2014; **14**:379.
32. Durham MD, Buchacz K, Richardson J, Yang D, Wood K, Yangco B, *et al*., and the HOPS investigators. **Sexual risk behvavior and viremia among men who have sex with men in the HIV outpatients study, United States, 2007–2010.** *AIDS* 2013; **63**:372–378.
33. Mattson CL, Freedman M, Fagan JL, Frazier EL, Beer L, Huang P, *et al*. **for the Medical Monitoring Project. Sexual risk behaviour and viral suppression among HIV-infected adults receiving medical care in the United States.** *AIDS* 2014; **28**:1203–1211.
34. Malek R, Mitchell H, Furegato M, Simms I, Mohammed H, Nardone A, *et al*. **Contribution of transmission in HIV-positive men who have sex with men to evolving epidemics of sexually transmitted infections in England: an analysis using multiple data sources, 2009–2013.** *Eurosurveillance* 2015; **20**:pii 21093.
35. European Centre for Disease Prevention and Control. *STI and HIV prevention in men who have sex with men in Europe.* Stockholm: ECDC; 2013.
36. Speakman A, Rodger A, Phillips AN, Gilson R, Johnson M, Fisher M, *et al*. **The 'Antiretrovirals, Sexual Transmission Risk and Attitudes' (ASTRA) Study. Design, methods and participant characteristics.** *PLoS ONE* 2013; **8**:e77230.
37. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy. 2012. http://www.bhiva.org/HIV-1-treatment-guidelines-2012.aspx.
38. Zou G. **A modified Poisson regression approach to prospective studies with binary data.** *Am J Epidemiol* 2004; **159**:702–706.
39. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA for the Ambulatory Care Quality Improvement Project (ACQUIP). **The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking.** *Arch Intern Med* 1998; **158**:1789–1795.

40. Daskalopoulou M, Rodger A, Phillips AN, Sherr L, Speakman A, Collins S, *et al*. **Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study.** *Lancet HIV* 2014; **1**:e22–e32.
41. Rodger AJ, Lampe FC, Grulich AE, Fisher M, Friedland G, Phanuphak N, *et al*. **for the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) START Study Group. Transmission risk behaviour at enrolment in participants in the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial.** *HIV Med* 2015; **16 (Suppl 1)**:64–76.
42. Crepaz N, Marks G, Liau A, Mullins MM, Aupont LW, Marshall KJ, *et al*. **for the HIV/AIDS Prevention Research Synthesis (PRS) Team. Prevalence of unprotected anal intercourse among HIV-diagnosed MSM in the United States: a meta-analysis.** *AIDS* 2009; **23**:1617–1629.
43. Hickson F, Bourne A, Weatherburn P, Reid D, Jessup K, Hammond G. *Tactical dangers: findings from the United Kingdom Gay Men's Sex Survey, 2008*. London: Sigma Research; 2010.
44. c JT, Schrimshaw EW, Wolitski RJ, Halkitis PN, Purcell DW, Hoff CC, *et al*. **Sexual harm reduction practices of HIV seropositive gay and bisexual men: serosorting, strategic positioning, and withdrawal before ejaculation.** *AIDS* 2005; **19 (Suppl 1)**:S13–S25.
45. Jin F, Crawford J, Prestage GP, Zablotska I, Imrie I, Kippax SC, *et al*. **Unprotected anal intercourse, risk reduction behaviours, and subsequent HIV infection in a cohort of homosexual men.** *AIDS* 2009; **23**:243–252.
46. Mao L, Kippax SC, Holt M, Prestage GP, Zablotska IB, de Wit JB. **Rates of condom and noncondom-based anal intercourse practices among homosexually active men in Australia: deliberate HIV risk reduction?** *Sex Transm Infect* 2011; **87**:489–493.
47. Bourne A, Reid D, Hickson F, Torres Rueda S, Weatherburn P. *The Chemsex study: drug use in sexual settings among gay & bisexual men in Lambeth, Southwark & Lewisham*. London: Sigma Research; 2014, www.sigmaresearch.org.uk/chemsex [Accessed March 2016].
48. Kelley CF, Haaland RE, Patel P, Evans-Strickfaden T, Farshy C, Hanson D, *et al*. **HIV-1 RNA rectal shedding is reduced in men with low plasma HIV-1 RNA viral loads and is not enhanced by sexually transmitted bacterial infections of the rectum.** *J Infect Dis* 2011; **204**:761–767.
49. The Swiss Statement and its repercussions. http://www.aidsmap.com/The-Swiss-Statement-and-its-repercussions/page/1746478/ [Accessed March 2016].
50. EACS European AIDS Clinical Society guidelines, version 7.1. 2014. http://www.eacsociety.org/guidelines/guidelines-archive/archive.html.
51. World Health Organization consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en/ [Accessed March 2016].
52. Persson A. **'The world has changed': pharmaceutical citizenship and the reimagining of serodiscordant sexuality among couples with mixed HIV status in Australia.** *Social Health and Illness* 2016; **38**:380–395.