Established in 1871

Swiss Medical Weekly

Formerly: Schweizerische Medizinische Wochenschrift

An open access, online journal • www.smw.ch

Appendix

The Swiss STAR trial – an evaluation of target groups for sexually transmitted infection screening in the sub-sample of men

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Original article | doi:10.4414/smw.2020.20392

Cite this as: Swiss Med Wkly. 2020;150:w20392 (Appendix)

Methods (long version)

We set up a country-wide multi-centre prospective observational cohort, offering free STI-testing to multi-partner men and women in Switzerland. Inclusion criteria were 16 years or older and three or more sexual partners in the last twelve months. The only exclusion criterion was antibiotic treatment in the past four weeks. The study provided follow-up examinations every six months. Apart from free STI-testing, we offered no additional financial incentives to study participants. The study was called STAR trial (STI-Testing for Asymptomatic individuals at Risk).

Online counselling tool / clients' questionnaire

Most voluntary counselling and testing (VCT) centres in Switzerland have been using the same online tool since April 2008, available in German, French, Italian, and English, and has since been amended to meet the needs of the centres using it and to fit the purpose of this study. Data is stored safely in compliance with national and European data protection laws. Clients receive a unique 9- to 10-digit alphanumerical code for identification at subsequent visits. For this study the code was printed on a study card and its use was mandatory at each visit. The VCT software has two password-protected logins: one is created every time the VCT centre initiates a case, using the clients' year of birth and postal code area. With this login, the clients can anonymously self-complete an online questionnaire on a tablet or desktop computer in the waiting room or at home before a scheduled visit. The client is asked to enter data on gender identity and genitals, sexual identity, detailed sexual history, previously diagnosed HIV or STIs, sexual happiness, mental health, drug use, risk and precautionary behaviour, including the numbers of sexual partners, STI testing and vaccination history. Completing the questionnaire takes 10–20 minutes. For each client seeking HIV/STI-testing in a participating centre, the online tool auto-checked eligibility based on the clients self-reported data and flagged eligibility to the health care professional.

The second login was for the health care professional to see certain key information necessary for planning of counselling and testing. In this study, health care professionals used the tool to document their interventions: STI tests, vaccinations, pre- and post-exposure prophylaxis for HIV, as well as information on STI test results, treatment and partner notification. Participants underwent the testing procedures, were asked to call-in for their results anonymously two days later (using the provided alpha-numerical code on their study card) and were asked to return in six months' time or when experiencing symptoms of STIs. In case of symptomatic STIs the testing procedure was similar, but the next follow-up visit was changed to six months after the symptomatic visit.

Five cantonal/regional ethical boards approved the study, and all participants gave informed consent before any study procedure was performed. Study information was available online as well as on paper in German, French, English, Spanish, Bulgarian, Hungarian, Romanian, and Russian.

Participating centres

All VCT centres in Switzerland [1], including the country's five gay health centres ('Checkpoints') and several organisations working with FSWs were approached and invited to participate, including two large drop-in health centres for FSWs in Zurich and Geneva. The centres received a bonus for including a pre-defined number of study participants at three months after local study initi-

ation, and a fee for each visit. Overall, 10 centres participated, among them two general hospitals (University Hospital Bern, Cantonal Hospital St. Gallen), four Checkpoints (Basel, Bern, Vaud, Zurich), three dedicated health centres for FSW (*Ladycheck*, Basel; *Isla Victoria*, Zurich, Walk-in Clinic Kanonengasse, Zurich), and PROFA, a private foundation offering sexual health services with eight centres in the Canton of Vaud. Outreach work for MSM was organised by the Cantonal Hospital St. Gallen in close collaboration with Swiss AIDS Federation, AIDS-Hilfe St.Gallen-Appenzell, *Mann-O-Mann* sauna in St. Gallen, *Moustache* sauna in Zurich. Outreach work for FSWs was organised by *Ladycheck*, *Isla Victoria*, and the Cantonal Hospital St. Gallen in collaboration with *Maria Magdalena*, an organisation providing counselling for FSWs in the canton of St. Gallen.

Recruitment

We recruited most men and women directly in VCT centres, triggered by website banners promoting free STI testing and word-of-mouth. MSM were also approached during local HIV/STI-testing outreach work in gay saunas. FSWs were also approached through outreach work in brothels. Participants were enrolled between January and December 2016, inclusion of FSW was extended until July 2017. Follow-up visits were possible until July 2017.

Laboratory

All centres were invited to collaborate with the study's central laboratory. Checkpoint Zurich engaged a different laboratory (identical methodology, 9% of all tests). At each baseline and follow-up visit, we systematically took a blood sample and performed pharyngeal, anorectal, and genital swabbing, regard–less of sexual history. Individuals with a vagina were vaginally swabbed or offered vaginal self-swabbing – equally effective but more acceptable [2] – alongside a one-page handout with visual instructions. Individuals with a penis were offered meatal swabs [3, 4] – penile self-swabbing was allowed upon request by known clients. In many cases the health care professional performed anorectal and pharyngeal swabbing, but self-swabbing was possible and accompanied by written instructions. All three swabs were then pooled to save costs. [5]

We used the Anyplex™ II STI-7 multiplex PCR assay from Seegene® for the detection of *N. gonorrhoeae* (NG), *C. trachomatis* (CT), *T. vaginalis* (TV), *M.genitalium* (MG), *M. hominis*, *U. urealyticum*, and *U. parvum* for pooled swabs (from pharynx, urethra, anus). Results of the last three bacteria mentioned are not reported as they are typically interpreted as commensal flora of the genital tract. [6] In addition to swabbing we performed antibody tests for HIV (HIV combi PT, ECLIA, cobas® 6000; module cobas® e601, Roche, Basel, CH) and *T. pallidum* (IgG/M Treponema screen, CLIA, Liaison® XL, DiaSorin, Saluggia, IT). Positive syphilis screening tests were confirmed by rapid plasma reagin (SYPHILIS RPR, flocculation quicktest, HUMAN, Wiesbaden, DE) as part of the study. Confirmation of reactive HIV screening tests – if not reflecting an already known diagnosis – was organised by the centre.

Baseline, but not follow-up visits, included tests for antibodies against hepatitis B surface antigen (HBs-AB) and the hepatitis C virus (HCV-AB)(Anti-HBs II and Anti-HCV II, ECLIA, cobas® 6000), followed by a confirmation test (HCV IgG recomLine, Mikrogen Diagnostik, Neuried, DE) and, if positive, HCV-RNA (HCV viral load, m2000 RealTime Systems, Abbott, Lake Bluff, US). In 06/2016, upon request of participating centres, we added antibodies against hepatitis B core antigen (HBc-AB) to the baseline package (Anti-HBc II, ECLIA, cobas® 6000).

All samples were labelled with the respective alphanumerical code, and for safety, the client's year of birth, postal code, and gender. The time needed for sampling, including the venous puncture, was approximately 15 minutes. Results were available two days later and had to be actively collected by the client. Treatment costs were not included in the study.

Other sexual health outcomes and sexualised drug use

The Swiss national online counselling tool includes a detailed list of symptoms, tailored to the participants' genitals: vaginal itching, abnormal vaginal discharge, foul-smelling odours; itching around the opening of the penis, penile discharge, pain and swelling of the testicles; spots or sores on the genitals, burning sensation when passing urine or during sex; pain on passing stool; dull pain in the rectum; rectal discharge.

It also covers two measures of sexual health other than HIV/STI diagnoses or symptoms: (1) sexual happiness ('Are you happy with your sex life?') with a 4-level Likert scale and a 5th item for people who sell sex ('I have no private sex life'), and (2) depression, measured with a short variant (PHQ-2) of the depression screening tool known as 'patient health questionnaire', with a reported sensitivity of 90–99% and a specificity of 53–62%. [7]

In recent years, certain forms of sexualised drug use (SDU) among gay men have become a new focus of research and activism, often referred to as 'chemsex'[8]. In this paper, we include two SDU measures – a more general one ('*Do you consume poppers, cannabis, cocaine or synthetic drugs before or during sex? – Yes/No')* and a more specific one ('chemsex'). The latter was introduced in 11/2016 and thus not available for most study participants at baseline. Participants who answered the general SDU questions with 'Yes', were asked additional questions on four specific substances, sometimes referred to as the '4-chems' [9]: *'In the last 12 months, have you consumed GHB/GBL (liquid ecstasy) / ketamine (special K) / Mephedrone (Meph,*

Miau) / Crystal (Meth, Tina)?'. For each checked substance, participants were asked: *'How often do you take (…)? – Rarely when I have sex / Often when I have sex / Always when I have sex*.' [10]

Statistical planning and analysis

All data analyses were performed using SPSS, v24. For all clinical outcomes, we provided two-sided 95% confidence intervals (CI); when the outcome was zero, we used the 'rule of three' [11] to estimate the upper limit of the 95% CI. To compare clinical outcomes between MSM/FSWs and their small comparison groups of other multi-partner men/women, we used Fisher's Exact Test for the calculation of exact p-values. To describe factors associated with STIs, we performed univariable and multi–variable logistic regression analyses and calculated adjusted Odds Ratios (AORs), setting overall significance at $p<0.05$. We used two composite endpoints: (1) active syphilis, NG, or CT; (2) any of the included STIs. To see if our models were valid for asymptomatic individuals, we performed a sensitivity analysis controlling for symptoms.

Switzerland's MSM population has been estimated at 80 000 (95% confidence interval: 64 000–96 000) individuals aged 15-64. [12] Based on published data with 10–13% of rectal swabs being positive for NG and CT [13], and assuming a drop-out rate of 25%, we calculated a minimum sample size of N = 430 for baseline and follow-up to achieve 80% power for prevalent and incident non-viral STIs. Based on a seroprevalence (HCV-AB) of 0.4% among MSM without diagnosed HIV [14], 520 MSM were needed to achieve 80% power to detect HCV in non-HIV-diagnosed MSM at baseline.

Estimating the size of Switzerland's FSW population is methodologically challenging, not least due to the high level of fluctuation (into and out of the country and/or between cities). The most frequently used estimate is 13 000–20 000. [15]

Based on a published STI prevalence of 7–19% among FSWs in Germany [16], we calculated a needed sample size of N = 400 to achieve 80% power for detecting non-viral STIs. We calculated with an assumed dropout rate of 50%, substantially under–estimating the turn-over of FSW in the study, and probably in the country.

Figure S1: Percentages of confirmed diagnosis of syphilis, gonorrhoea, or chlamydia in the **'men' part of the STAR trial**, by numbers of sexual partners (previous 12 months) and consistency of condom use for anal/vaginal sex (previous 3 months). N = 871. CAVI, condomless anal or vaginal intercourse

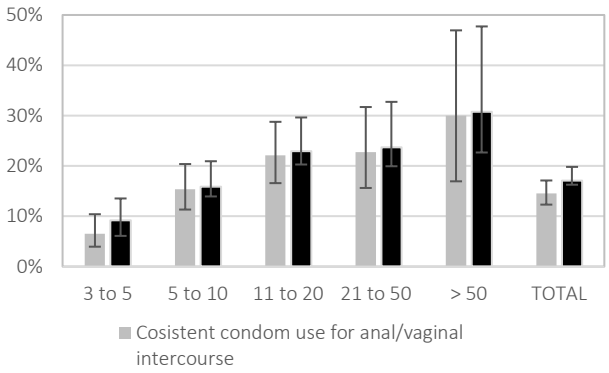

Table S1: Comparison of prevalence rates for HIV, syphilis, gonorrhoea, C. trachomatis, and hepatitis B in the FSW part of the STAR trial with findings from the ASPASIE study [17] in Geneva (March 2017-March 2019). The ASPASIE study did not provide 95%-confidence intervals, so we calculated them to increase comparability of the results.

PREVALENCE AT BASELINE	*STAR trial (2015–17) % (95%-CI)*	*ASPASIE study† (2017–19) % (95%-CI)*
FSWs with baseline visit	N = 490	N = 258
All prevalent HIV	0.4 (0.1–1.6)	0.4 (0.0–2.5)
Active syphilis (treatment)	1.2 (0.5–2.8)	0.8 (0.1–3.1)
T. pallidum IgG/M positive	5.9 (4.1–8.5)	5.4 (3.1–9.1)
N. gonorrhoeae	4.9 (3.2–7.3)	2.0 (0.6–5.3)
C. trachomatis	6.3 (4.4–9.0)	5.9 (3.2–10.3)
HBc-AB positive, HBs-AB negative	1.4 (0.8–1.8)	†0.0 (0.0–1.2)

CI, confidence interval; FSW, female sex worker. †In the ASPASIE study, antibodies for HIV and T. pallidum were measured with SD BIOLINE HIV/Syphilis Duo® rapid test; active HBV infection was measured by the prevalence of hepatitis B virus surface antigen (Vikia® HBs-Ag rapid test). Individuals positive for HBs-Ag are a sub-group of those with the marker for uncleared infection, the marker used in the STAR trial is thus necessarily higher than the marker used in the ASPASIE study.

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