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Smartphone app and carbon monoxide self-monitoring support for smoking cessation: A randomised controlled trial nested into the Swiss HIV Cohort Study

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Running head: CO self monitoring for smoking cessation

Author contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval of the version to be published. DG; HCB and FC had access to the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis. HCB, AN, DG; were involved in the conception and design of the study and data interpretation. DG was responsible for conducting the trial. DG and FC were responsible for data analysis. MS, AD, DLB, HF; NBB, EB and PS were involved in the acquisition of data. DG and HCB wrote the manuscript and all co-authors contributed to final version. HCB acquired funding for the study.

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Smoking related cardiovascular morbidities and cancers are increasing in HIV positive individuals due to improved prognosis of HIV infection and high prevalence of smoking. More effective smoking cessation programs are therefore needed [1-3]. Evidence from interventional trials indicates that self-monitoring techniques and motivational support by mobile phone-based text messaging may increase quit rates in smokers [4;5]. Self-monitoring of exhaled carbon monoxide (CO) measurement is a novel approach that may assist motivated smokers to quit.

We investigated whether CO self-monitoring in conjunction with a smoking cessation app may improve smoking cessation in HIV positive smokers. We nested a randomized controlled into the Swiss HIV Cohort Study [6], and randomly allocated during biannual cohort visits patients smoking ≥ 3 cigarettes a day via a trial website to counselling by SHCS centre physicians (usual care) or to a combined intervention of CO self-monitoring with mobile phone based feedback and app based smoking cessation support. All participants had to provide informed consent to trial participation and fix a quit date within a 2 weeks period from the randomisation date. All trial participants irrespective of randomisation received standard smoking cessation care consisting of short smoking cessation advices by treating

centre physicians, voluntary referral to smoking cessation clinics, and nicotine replacement therapy at physician discretion.

Study nurses assisted patients in the intervention group to download the Smokerlzyer® and Stop-tabak apps (www.stop-tabak.ch) on their personal mobile phones and assured the patient's registration via a secured channel in the patient communication platform (Jaymob, Jackson Mobile Berlin GmbH, Germany) which allowed to activate the iCO Smokerlyzer® communication mode. The platform allowed to monitor all CO measurement in a webserver that was hosted in a T-system cloud environment and to send reminder messages for CO measurements. The IT company provided regular downloads by patient ID with the CO measurement, the corresponding dates, and the dates of sent text reminders which were transferred to a secured trial data base on the server of the University Hospital Basel.

Patient were instructed how to connect the iCO™ Smokerlyzer® (Bedfont Scientific Ltd, England) CO monitoring device with their mobile phone and how to measure the CO content in exhaled air. The iCO Smokerlyzer® is a breath test carbon monoxide monitor with a replaceable mouth cap intended for single users and serves as a motivational tool to encourage smoking cessation. It connects via a USB or headphone plug-in connector to newer generation mobile phones and measures the CO content in the exhaled air. Instant readings are downloaded via app to a personal profile on the phone. Depending on the results of the breath test, individualized messages are delivered to enhance maintenance of abstinence or increase the motivation to quit. Trial participants received text messages with a request to use the personal CO monitor Smokerlyzer® daily for the first 4 weeks, twice weekly for the following 4 weeks and once weekly from the beginning of the third month to the end of the trial.

The Stop-tabac.ch app provides advices in all Swiss national languages and English for quitting, coping with withdrawal symptoms and relapses and is supported by the Swiss Ministry of Health [7] and was used and a supplementary intervention tool in this trial. It offers

a coaching function where users receive personalized messages that encourage smoking cessation and give advice for behavioural change. The app offers also options to seek support from friends and family and a forum for discussing smoking cessation related issues with peers.

By virtue of the nested trial design all demographic and clinical baseline data and self reported smoking data relevant to this trial at baseline and 6 months follow-up were collected via routinely biannual cohort visits [6]. The primary outcome was the combination of self-reported continuous abstinence biochemically verified at 6 months by an in-person carbon monoxide, with a cut-off of CO in exhaled air of 7 parts per million (ppm) (piCO Smokerlyzer CO, Bedfont Scientific Ltd, England) that was done by nursed not blinded for treatment status. Self-reported continuous abstinence was defined as no more than five cigarettes smoked since the start of the abstinence period at 6 months of follow-up. The follow-up examination coincided with the next cohort visit. Self-reported continuous abstinence was assessed by physicians during routine 6-month follow-up and directly entered into the study's website. Participants reporting abstinence whose final CO test was positive were counted as smokers as were patients with loss of smoking status follow-up information. Secondary outcomes were differences in the number of daily cigarettes smoked from baseline to 6-month follow-up and point prevalence of abstinence (i.e. no smoking in the past 7 days) at 6-month follow-up.

Based on self reported quit rates from users of the stopp tabab.ch app (8%) we assumed that our combined intervention with additional CO self monitoring would lead to a sic months quit rate of 12 % and 5% in the control group, respectively. With a significance level of $\alpha = 0.05$ (two-sided) and a power of 0.8 a total of 496 patients were needed.

The primary intention to treat analysis was performed on the basis of a self-reported continuous abstinence (defined as no more than five cigarettes since the start of the abstinence

period) biochemically verified by a CO breath test at 6 months of follow-up. Patients with missing data or a positive CO breath test at 6 months follow-up were counted as smokers. Analysis was by logistic and linear regression for smoking cessation rates and difference in daily cigarette consumption at 6 months follow-up, respectively with adjustment for past self-reported history of smoking cessation, numbers of cigarettes smoked at trial start, and prescribed nicotine replacement or drugs against withdrawal symptoms. All analyses were done in R version 3.5.2. The trial protocol was approved by Swiss Ethcs and registered at ClinicalTrials.gov, ID NCT02840513.

At the start of the trial on June 1st 2017 3293 of 10,493 (34%) patients in the SHCS smoked ≥3 cigarettes and these 2444 (74%) indicated at any cohort visit in the previous 48 months to have quit once and then resumed smoking. During a recruitment period of 1.5 years, 1807 patients were screened for inclusion and a total of 81 patients were enrolled (Figure 1). Trial participants compared to the remaining smoking population in the SHCS were better educated, had more previous quit attempts, smoked more cigarettes and were more frequently men having sex with men (MSM), but less frequently IV drug users (Table 1). Six of 42 (14%) participants in the intervention group and five of 39 (13%) in the standard of care group quit smoking at 6 months follow-up (adjusted OR 1.06, 95% CI 0.29; - 3.86) and three participant were lost to follow-up. Based on 12 months cohort data one individual had resumed smoking and five trial participants reported to have quit smoking. The adjusted mean difference in smoked cigarettes between the intervention and control groups at 6 months was -1.38 (95% CI -4.45; 1.69).

In total 24 (57%) and 18 (46%) patients in the intervention and control groups received nicotine replacement therapy. Eleven (26%) of the participants in the intervention group sent at least one result of a CO measurement with the Smokerlyzer App (median 22.5 (IQR 6- 63)). Twelve (28.5%) participants in the intervention group reported using the Stop-tabac.ch app

multiple times a week during the first month of the intervention. Of all the remaining smokers in the cohort who did not participate in the trial, 53 (1.6%) had reported during the trial recruitment period not to be smoking at the next 6 months cohort visit and 78 (2.4%) at the 12 months visit. The trial was terminated prematurely due to insufficient patient recruitment and lack of funding.

Results from this pragmatic trial remained inconclusive and underpowered due to recruitment difficulties although the nested trial design allowed for the potential to recruit from a large group of smokers with a self reported history for quitting. Patients included in the trial reported more cessation attempts than non-participants which was identified as the best predictor for successful quitting from observational data analysis of the SHCS [8]. This information, however, did not translate into a high recruitment rate. Forcing patients to fix a quit date in a time window of two weeks following the cohort visit may have distracted not optimally motivated patients ready to immediately try to quit. Installation of smoking cessation and CO monitoring apps was time consuming and many patients indicated difficulties in using the CO monitoring device. The high variety of mobile phone models and operating systems created compatibility problems with the CO device, some of which were hard to identify during the initial setup and installation. Integrating this intervention into the routine of busy infectious disease clinics turned out to be very demanding for clinicians and staff. Nevertheless, 11% of the trial population – irrespective of the intervention – quit which is considerable higher than the 1.6% smokers in the remaining cohort who had indicated to have quit.

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Members of the Swiss HIV Cohort Study

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Figure 1 Trial Profile

Table 1 Baseline characteristics of trial participants and of the entire smoking population in the Swiss HIV Cohort Study

	Trial participants	Intervention	Control	Smokers in cohort
Randomized to trial/ entire cohort (n)	81	42	39	3293
Males (n, %)	68 (84%)	36 (86%)	32 (82%)	2489 (76%)
Age (median (IQR))	47 (40-52)	47.5 (41-52)	47 (40-52)	50 (42- 550)
Education ≥ 9 years (n, %)	62 (77%)	31 (74%)	31 (80%)	2338 (74%) [+]
Pack years (median (IQR))	15 (9-25)	15 (9-26)	16 (7.5-24)	18 (10- 25) [§]
Cigarettes smoked (median (IQR))	17 (10-20)	15.5 (10-20)	20 (10-20)	15 (10-20)
Previous attempt to quit smoking (n, %)	23 (28%)	12 (29%)	11 (28%)	695 (21%)
Framingham risk score				
<10%	48 (59%)	25 (59.5%)	23 (59%)	1855 (56.3%)
10-19%	25 (31%)	14 (33.3%)	11 (28%)	985 (30%)
>20%	6 (7.5%)	2 (4.8%)	4 (10%)	449 (13.6%)
missing	2 (2.5%)	1 (2.4%)	1 (3%)	4 (0.1%)
Previous CV event (n, %)	10 (12%)	7 (17%)	3 (7.7%)	301 (9.1%)
On ART (n, %)	81 (100%)	402 (100%)	39 (100%)	3169 (96%) [ǂ]
Previous AIDS event (n, %)	14 (17%)	6 (14%)	8 (21%)	721 (22%)
CD4 start cells/µl (median (IQR))	732 (540-960)	754 (537-975)	696 (556-936)	704 (507-926) [¥]

RNA viral load >20 copies/ml (n, %)	8 (10%)	3 (7%)	5 (13%)	321 (10%)[5]
RNA viral load >400 copies/ml (n, %)	2 (2.5%)	1 (2.6%)	1 (2.4%)	98 (3%) [¢]
Current IV drug use (n, %)	7 (9%)	3 (7%)	4 (10%)	359 (10.9%)
Source of infection (n, %)				
Men having sex with men	41 (51%)	22 (52%)	19 (49%)	1433 (44%)
Heterosexual	27 (33%)	16 (38%)	11 (28%)	983 (30%)
Intravenous drug use	9 (11%)	2 (5%)	7 (18%)	732 (22%)
Other source	4 (5%)	2 (5%)	2 (5%)	145 (4%)

[+] Missing 122 values; [§] Missing 249 values; [ǂ] Missing 36 values; [¥] Missing 17 values; [¢] Missing 31 values

Baseline for trial participants refers to the date of randomisation and for the cohort population to the date of trial start

Figure 1 Trial Profile