

An Adherence-Enhancing Program Increases Retention in Care in the Swiss HIV Cohort

Susan Kamal,^{1,2,3,4} Tracy R. Glass,^{4,5,6} Thanh Doco-Leconte,⁶ Sophie Locher,^{1,2} Olivier Bugnon,^{1,2,3,7,8} Jean-Jacques Parienti,⁸ Matthias Cavassini,^{9,10} and Marie P. Schneider^{1,2,3,11}

¹School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland ²Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, Geneva, Switzerland ³Center for Primary Care and Public Health (Unisanté), University of Lausanne, Lausanne, Switzerland, ⁴Clinical Statistics and Data Management Group, Swiss Tropical and Public Health Institute, Basel, Switzerland, ⁵University of Basel, Basel, Switzerland, ⁶HIV Unit, Department of Internal Medicine, Geneva University Hospital, Geneva, Switzerland, ⁷Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland, ⁸Hospital Center University De Caen, Caen, France, ⁹Infectious Disease Service, Lausanne University Hospital, University of Lausanne, Lausanne Switzerland

Background. This study tested a theory-based adherence-enhancing intervention: the “Interprofessional Medication Adherence Program” (IMAP) to increase human immunodeficiency virus (HIV) retention in care.

Methods. We retrospectively compared our intervention center (intervention group [IG]) with a standard of care center (control group [CG]) both participating in the Swiss HIV Cohort Study between 2004 and 2012. Endpoints were defined as >6-month and >12-month gaps in care for intervals of care longer than 6 and 12 months without any blood draw. Inverse probability of treatment weights was used to adjust for differences between patients at the 2 centers. Viral failure was defined as ribonucleic acid ≥ 50 copies/mL after 24+ weeks on antiretrovirals.

Results. The IG included 451 patients, CG 311. In the IG, 179 (40%) patients took part in the IMAP for a median of 27 months (interquartile range, 12–45). Gaps in care of ≥ 6 months were significantly more likely to happen in the CG versus IG (74.6% vs 57%, $P < .001$). The median time until the first treatment gap was longer in the IG vs CG (120 vs 84 weeks, $P < .001$). Gaps in care of ≥ 12 months evaluated in 709 (93%) patients were significantly more likely to occur in the CG compared with the IG (22.6% vs 12.5%, $P < .001$). The rate of viral failure was significantly lower in the IG (8.3% vs 15.1%, $P = .003$).

Conclusions. This study, in a real-world setting, shows the effectiveness of the IMAP to reduce 6- and 12-month gaps in follow up among people with HIV. These results should be confirmed by studies in other settings.

Keywords. adherence intervention; antiretrovirals; HIV; interprofessionalism; medication retention in care.

Due to the success of combined antiretroviral therapy (cART), human immunodeficiency virus (HIV) has become a chronic illness that can be managed successfully [1], but it requires people with HIV (PWH) to engage in a lifelong continuum of healthcare services and medication adherence. People with HIV that disengage from care or fail to adhere to their cART develop significant morbidity and mortality [2]. Low rates of retention in care have dramatic consequences for patients’ health [3] as well as public health risks such as increased resistance and transmission rates [4]. In 2016, the retention in HIV medical care among

PWH was 57.6% in the United States [5]. Adherence to cART is the last step in the cascade of care as described by Gardner et al [6]; it reflects retention and engagement in care. Indeed, adherence to cART is crucial to achieve desirable individual-level health outcomes such as suppression of viral load and increase in CD4 count [7, 8].

Scalable interventions are needed to sustain low HIV infectiousness by improving HIV treatment adherence and retention in care. Successful interventions that manage to engage and retain PWH in care are not only beneficial to those individuals but also for the public health. Evidence shows that patients retained in care and adherent to their medication reduce risk of transmission behaviors are more likely to be virally suppressed [9, 10].

Medication adherence is generally defined as the extent to which patients take their medication regimen as prescribed by their healthcare providers [11]. It has 3 phases: (1) initiation, which marks the start of the treatment; (2) implementation, which marks the extent to which the patient follows the dosing regimen; and finally (3) discontinuation, which marks the interruption of treatment [12]. Nonadherence can occur in any of those phases such as non- or long-term delayed initiation,

Received 29 April 2020; editorial decision 23 July 2020; accepted 10 August 2020.

¹M. C. and M. P. S. are equal senior contributors.

Presented in part: IAPAC, June 2017, Miami, FL.

Correspondence: Marie P. Schneider, PhD, Professorship of Medication Adherence and Interprofessionalism, School of Pharmaceutical Sciences, University of Geneva, CMU-B05, bureau B05.17.17.B, Rue Michel-Servet 1, 1211 Genève 4, Switzerland (marie.schneider@unige.ch).

Open Forum Infectious Diseases®

© The Author(s) 2020. Published by Oxford University Press on behalf of Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDeriv licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
DOI: 10.1093/ofid/ofaa323

suboptimal implementation, or premature interruption of treatment, defined as nonpersistence [12]. As a result, it is important to develop effective interventions at different levels of the HIV care continuum [13].

Despite that there is no gold standard for measuring retention in care [14], studies have shown the strong prognostic value of missed visits for clinical events and mortality [15]. Missed medical visits have been associated with higher mortality in comparison with PWH who did not miss scheduled visits [4].

This study tests a theory-based cognitive behavioral intervention to increase HIV treatment engagement and retention. Our study hypothesis is that the interprofessional medication adherence program (IMAP) has the ability to increase retention in care by reinforcing pharmaceutical care as well as coordination of care between pharmacists, physicians, and nurses.

METHODS

Medical Setting

This is a retrospective study that compared data collected in routine care from a tertiary HIV disease center running a medication adherence intervention program in Lausanne with a comparative tertiary HIV center in Geneva without a medication adherence program. The HIV clinic in Geneva offers follow-up consultations to approximately 600 patients per year and is run by 2.4 full-time equivalent junior doctors and 1 full-time senior physician. The HIV clinic in Lausanne offers follow-up consultations to 850 patients per year and is run by 3 full-time equivalent junior doctors and 1 full-time equivalent senior physician.

Medical follow up is similar in both centers, which are located 70 km apart in the same linguistic area of Switzerland. Both hospitals are participating centers of the Swiss HIV Cohort Study (SHCS), an ongoing, multicenter, prospective, observational study for interdisciplinary HIV-related research [16]. Both centers propose the same follow-up standards, questionnaires, laboratory tests, and physical exams. Medical directors meet every 3 months at the scientific board of the SHCS to discuss protocols and best medical practice. Every 6 months, at the patient visit, physicians of both centers fill in the SHCS case report forms that cover all of the social and medical outpatient assessments. Both centers also collect biannual, physician-assisted, self-reported adherence assessments [17]. Both centers follow their patients more frequently during the first year of treatment according to the International AIDS Society guidelines. Data collected during each single additional visit, including CD4 count and HIV viral load, are transferred to the SHCS data base.

The start date of the study was 2004, the date of start of the medication adherence program in Lausanne. The study end date was the end of 2012 as Geneva started an intervention

aimed at improving clinical attendance (Short Message Service [SMS] reminders in routine care) in 2013 [18].

Participants

All adult PWH (>18 years old) attending the Lausanne or Geneva centers between 2004 and 2012 for at least 6 months, starting antiretroviral therapy (ART) in 2004 or later, were considered as eligible.

Control Center

All eligible SHCS patients in the Geneva center were included in the control group (CG). In the CG, standard of care for reinforcing retention in care consisted in sending 1 letter as a reminder to missed appointments for physical and clinical check-ups [16].

Intervention Center

All eligible SHCS patients in the Lausanne center were included as belonging to the intervention group (IG) even though only a subset (40%) participated in the adherence program. This was done since an intervention by design only includes those who need it.

Medication Adherence Program

In the Lausanne center, pharmacists of the Center for Primary Care and Public Health, in collaboration with the Infectious Diseases service of the University Hospital, implemented an interprofessional medication adherence support program (IMAP) in 2004. The program is fully described elsewhere [19–22]. Medication adherence is monitored via electronic monitors (EMs) (MEMS and MEMS AS; AARDEX Group, Sion, Switzerland), fitted with a digital display showing the number of openings day by day to the patient; EM is combined with manual pill count. During motivational interviews (MIs), electronic adherence data, in the form of a chronology plot, is shown to the patient as feedback every 30 to 90 days depending on patients' needs, and a report is sent to the physician after each interview to ensure continuity in care. All adherence moderating factors are discussed during the MI in a comprehensive approach [23]. Patients are referred to social or psychological aid if needed.

The selection of patients to participate in the medication adherence program is done through shared decision making between the infectious disease (ID) physicians and the patients. Most patients who are referred to the adherence program are those with adherence difficulties or those at risk of adherence difficulties due to psychosocial issues at cART initiation, when cART is changed or at any time during the follow up. Presence of 6- and 12-month gaps in care was not used as a measure to direct patients to the adherence program.

Patients remain enrolled in the medication adherence program as long as needed to help them achieve and maintain a sufficient level of adherence, until all the barriers to adherence are addressed and viral load is undetectable. This is determined through shared decision making between the healthcare providers (HCPs), in particular the pharmacist and the physician, and the patients.

For all patients recently lost to follow up in the medication adherence program, reminders (2 phone calls and 1 letter) and rescheduling of missed appointments are done. In addition, there is a bimonthly interprofessional discussion between the pharmacists, physicians, and nurses on patients who were lost to follow up within the past 8 weeks.

The medication adherence program is run by a team of 1.2 full-time equivalent pharmacists, 1 full-time pharmacy technician, and 0.4 full-time equivalent senior pharmacist. All the pharmacists involved in the adherence program are educated in medication adherence management and are trained in MI [19].

Data Analysis

Baseline was defined as the date of cART initiation. Baseline sociodemographic and clinical variables were described according to center using percentages or median and interquartile ranges (IQRs) as appropriate.

Several methods have been used to measure retention in care including measurement of CD4 count and viral load, missed medical visits, and gaps in care [24, 25]. All laboratory and medical visits are captured and stored systematically in the available SHCS database. After the first year of treatment, visits are conducted on a semiannual basis and include a blood draw 7 to 14 days earlier [26, 27]. Gaps in care were defined as gaps in blood draws lasting more than 6 or 12 months in duration. We used gaps in blood draws rather than gaps in medical visits because blood draws occur more systematically than medical visits. The length of the gap in care is the number of weeks between patients' last blood draw and their return to care, stop date, or censoring date. Stop date was defined as the date of the last visit (eg, before the patient was transferred to another clinic). The censoring date was the administrative closure of the database, which was on December 31, 2012. The incidence of gaps, length of the gaps, and time until the first gap in care were also calculated. The percentage of patients with gaps was compared using χ^2 test. The median length of the gap and the median time until the first gap in care were compared using Wilcoxon rank-sum test.

Individuals in the SHCS are asked biannually about missed doses of cART in the last 4 weeks (daily, more than once a week, once a week, once every second week, once a month, never) through the SHCS physician-assisted-self-reported adherence questionnaire (SHCS-AQ). Because the specificity of nonadherence as measured by self-report is high, adherence was summarized over the study period by calculating the worst

self-reported adherence. It was compared among centers (IG vs CG) using χ^2 test. In the IG, we compared outcomes according to whether participants were included in the medication adherence program (IMAP) using χ^2 tests.

We also assessed viral failure as an outcome. It was defined as HIV ribonucleic acid (RNA) ≥ 50 copies/mL in the plasma after a minimum of 24 weeks on cART and was compared among centers using χ^2 test.

Because the intervention was allocated at the level of center and not individual, it is important to adjust for differences in the patient populations at the 2 centers to understand the potential effect of the intervention. We initially compared retention in care before the study (1999–2003) between the centers and changes in retention in care both within and across centers. In addition, we controlled for differences between the 2 centers using several methods, including multivariate models, propensity score, inverse probability of treatment weighting (IPTW), and indirect standardization ratio ([ISR] also called “standardized-mortality ratio”) [28–31]. Specifically, the IPTW model estimates the intervention effect in a population, whose risk factors are equal to that of all study participants. The ISR-weighted model estimates the intervention effect in a population, whose risk factors are equal to that found in the intervention participants only.

Variables included in the multivariable analyses were chosen a priori and included irrespective of significance: age, gender, ethnicity, citizenship, education, income source, risk groups for HIV infection, depression, psychiatric problems, smoking, living alone, hepatitis B, hepatitis C, CD4 at cART start, acquired immune deficiency syndrome (AIDS), prior treatments with cART, cART classes, and years living with HIV. Statistical analyses were performed in SAS 9.3 (SAS Institute, Cary, NC).

Patient Consent Statement

All patients who are part of the SHCS have given their written consent to use their data for research purposes. The research proposal of this study was approved by the scientific board of the SHCS on August 27, 2014.

RESULTS

There were 762 individuals who started cART between 2004 and 2012: 451 in the IG and 311 in the CG. Fifty-five percent of individuals had received cART before registration into the SHCS for a median of 32 weeks (IQR, 10–94). In the IG, 179 (40%) took part in the medication adherence program at any time during the study period for a median of 27.5 months (IQR, 12.3–45.3).

Baseline characteristics of participants are presented in [Table 1](#). Participants at the 2 centers differed in terms of ethnicity, citizenship, education, smoking, hepatitis C, and prior ART treatment.

Table 1. Baseline Characteristics^a

Characteristics	Intervention, n = 451	Standard Care, n = 311
Male, n (%)	281 (63.3)	194 (62.4)
Age, median (IQR)	37 (30–45)	36 (30–44)
Nonwhite, n (%)	184 (40.8)	165 (53.1)
Swiss nationality, n (%)	162 (35.9)	91 (29.3)
Higher education, n (%)	125 (27.7)	150 (48.2)
Has income from working, n (%)	451 (100)	311 (100)
Psychiatric problems, n (%)	38 (8.4)	22 (7.1)
Legal problems, n (%)	3 (0.7)	0 (0)
Living alone, n (%)	155 (34.4)	117 (37.6)
Smoker, n (%)	184 (40.8)	102 (32.8)
Hepatitis C coinfection, n (%)	66 (14.6)	23 (7.4)
Mode of transmission, n (%)		
MSM	141 (31.3)	81 (26.1)
Heterosexual	244 (54.1)	190 (61.1)
IVDU	42 (9.3)	19 (6.1)
Other/Unknown	24 (5.3)	21 (6.8)
AIDS, n (%)	80 (17.7)	62 (19.9)
CD4 cells, median (IQR)	246 (127–330)	252 (139–356)
Prior ART treatment, n (%)	174 (38.6)	215 (69.1)
Duration of prior ART (weeks), median (IQR)	40 (16–102)	32 (10–95)
EM use, n (%)	179 (40)	0 (0)
Duration of follow-up under EM (months), median (IQR)	27.5 (12.3–45.3)	-
ART class, n (%)		
NNRTI	238 (52.8)	184 (59.1)
PI	121 (26.8)	78 (25.1)
Boosted PI	70 (15.5)	29 (9.3)
Other	22 (4.9)	23 (7.4)
Self-Reported Adherence, n (%)		
Never missed a dose	230 (53)	190 (65)
Once a month missed dose	124 (28.6)	39 (13.5)
Once every second week missed dose	26 (6)	16 (5.6)
Once a week missed dose	19 (4.4)	16 (5.6)
More than once a week missed dose	22 (2.1)	20 (6.9)
Daily missed dose	12 (2.7)	7 (2.4)

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; EM, electronic monitor; IQR, interquartile range; IVDU, intravenous drug user; MSM, men who have sex with men; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

^aBaseline is the first follow-up visit closest to the date of starting ART.

Between 1999 and 2003, 164 individuals started cART: 84 in the IG and 80 in the CG. Retention in care was similar between the groups: gaps in care of ≥ 6 months occurred in 81% of IG and 76% of CG ($P = .5$), and gaps in care of ≥ 12 months occurred in 51% of IG and 50% of CG ($P = .88$).

During the 2004–2012 study period, 64.2% patients had a gap of care of longer than 6 months after a median of 106 weeks of treatment (IQR, 55–175) and lasting a median of 30 weeks (IQR, 27–38), ie, 4 weeks longer than the expected 26-week interval. Individuals in the CG were significantly more likely to have a gap in care longer than 6 months compared with the IG (74% vs 57%, respectively, $P < .001$). The time until the first treatment gap was significantly longer in the IG ($P < .001$), but gaps were not different in length (3.2 vs 5 weeks, $P = .23$) between the IG and CG. Within the intervention center, the incidence of visit

gaps was significantly reduced in those who took part in the medication adherence program versus those who did not (45% [$n = 179$] vs 65% [$n = 132$] participants, $P < .001$). There were more individuals on cART before the registration in the SHCS in the CG versus IG. Individuals who were on cART before registration with the SHCS were more likely to have a treatment gap (66% vs 61%, $P = .12$), but the difference was not significant. The effect of the intervention remained significant in the subset of participants with no prior cART ($n = 339$, 56% [$n = 190$] vs 73% [$n = 247$], $P = .004$).

Gaps of 12 months could be evaluated in 709 (93%) participants. Of these, 16.6% had a gap of care of longer than 12 months after a median of 86 weeks of treatment (IQR, 46–192) with a length of the gap lasting a median of 72 weeks (IQR, 59–117), ie, 14 weeks longer than the expected 52-week

interval. Gaps of 12 months were significantly less likely in the IG compared with the CG (12% vs 22%, $P < .001$). The time until the first treatment gap ($P = .57$) and the length of the gaps ($P = .16$) were not significantly different between groups. In the intervention center, there were fewer visit gaps in those who are part of the intervention versus those who are not (10% vs 13%, $P = .36$); however, the difference was not significant. The occurrence of 12-month gaps was significantly higher in individuals who were on cART before registration with the SHCS cohort (20% vs 11%, $P = .003$); however, the effect of the intervention was no longer significant in the subset of patients with no prior cART ($n = 322$; 12% [$n = 39$] vs 11% [$n = 35$]; $P = .76$). **Figure 1** shows the probability of absence of treatment gaps over time since cART start.

Self-reported adherence data were available in 95% of participants. Overall, 58% of individuals reported never missing a dose of ART during the study period. The distribution of the worst reported adherence varied according to center with those at the IG more often reporting missed doses (47% versus 34%, $P < .001$). In the IG, worst reported adherence did not differ significantly in those who were part of the intervention versus those who were not ($P = .18$).

The rate of viral failure was 11% overall and was significantly lower in the IG (8.3% vs 15.1%, $P = .003$). Viral failure rates did not differ in IG in those who were part of the intervention versus those who were not ($P = .67$). Thirty-three percent (33%) of viral failures happened after the first 6-month gap.

This percentage was higher in the IG (41% vs 28%, $P > .05$) but is not significant. There was an association between viral failure and treatment gaps (76% of those with viral failure also had a treatment gap vs 62% of those without viral failure, $P = .01$).

Several methods were used to adjust for the differences in the patient populations at the centers (see **Tables 2** and **3**). Both logistic regression models for the probability of a 6- and 12-month gap and survival models for the time to a 6- and 12-month gap are presented for comparison.

The average propensity score for those in the IG was 0.68 (standard deviation [SD] = 0.19) compared with 0.46 (SD = 0.22) for those in the CG. The average IPTW weights for those in the IG was 1.67 (SD = 0.81) compared with 2.46 (SD = 2.10) for those in the CG. All >6- and >12-month models produced similar significant results except for the 12-month ISR-weighted model, which showed a nonsignificant difference in retention in care between both groups.

DISCUSSION

We evaluated the effectiveness of the IMAP to minimize loss to follow up and increase retention in care. Confirming our study hypothesis, the intervention seems to have the ability to limit 6- and 12-month gaps of follow up. Our results also show that patients who had treatment gaps were more likely to be at risk of viral failure even though the level of viral failure in both centers was contained to 11% overall.

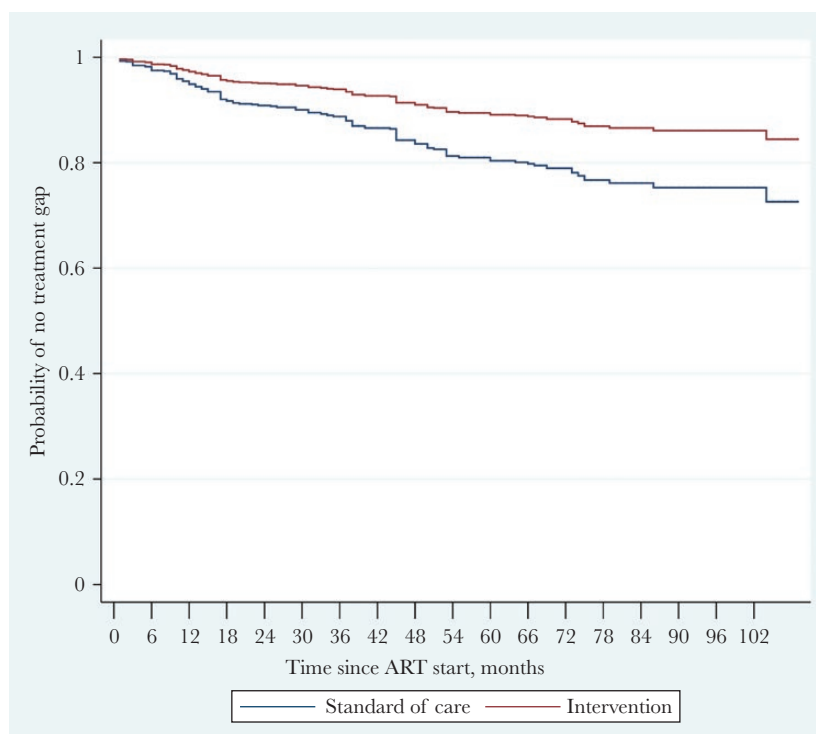


Figure 1. The probability of treatment gaps over time since combined antiretroviral therapy (ART) start (according to inverse probability of treatment-weighted model).

Table 2. Effect of the Intervention on 6-Month Treatment Gaps Comparing Different Methods to Adjust for Different Patient Populations at the Two Centers

Methods	N	OR (95% CI)	P	HR (95% CI)	P
Crude	759	0.45 (0.33–0.62)	<.001	0.62 (0.52–0.75)	<.001
Adjusted for covariates	634	0.41 (0.27–0.64)	<.001	0.59 (0.48–0.73)	<.001
Adjusted for propensity score	634	0.51 (0.34–0.76)	.001	0.62 (0.50–0.76)	<.001
Adjusted for propensity score + covariates	634	0.45 (0.29–0.69)	<.001	0.61 (0.49–0.76)	<.001
IPTW model	634	0.43 (0.28–0.65)	<.001	0.67 (0.53–0.86)	.001
ISR-weighted model	709	0.35 (0.21–0.56)	.01	0.67 (0.51–0.88)	.004

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ISR, indirect standardization ratio; OR, odds ratio.

Contrasting with the lower viral failure in the IG, our results showed that patients in the IG were more often reporting missed doses than the CG in the SHCS questionnaire. This counterintuitive result can be due to the influence of the IMAP on ID physicians and patients in the intervention center. Our hypotheses is that physicians are more used to observing missed doses in the IMAP medication adherence feedback report and are therefore more overtly discussing the possibility of missing doses with their patients during the physician-assisted adherence questionnaire. Furthermore, it decreases the desirability bias and its collateral effects because patients are positively encouraged to talk on nonadherence events that were monitored electronically in the past weeks. This may make the patients more likely to report missed doses.

The evidence-based recommendations of the International Association of Providers of AIDS Care (IAPAC) for improving retention in care and cART adherence for PWH recommend the use of reminder devices and one-on-one patient counseling using specific adherence-related tools [32]. In our IG, 179 patients were referred to the medication adherence program. In case any patients missed an appointment of the medication adherence program, they received up to 2 phone calls and 1 reminder letter. Early missed appointment tracing is shown to reduce the loss to follow up of patients [33]. In addition, the incidence of 6-month visit gaps was significantly reduced in those who took part in the medication adherence program. Electronic monitors can serve as a reminder for the patients to take their medication as prescribed based on the LCD-display information of day-to-day dose intake. It can also serve as aid to tailored feedback using motivational interviewing to address patient ambivalence and to discuss the barriers and facilitators of their

adherence to cART; for example, regimen complexity, timing, side effects, how to organize cART intake when outdoors, when traveling, when drinking alcohol, or in a social company, and how to reschedule a missed dose or ensure regimen ritualization. Motivational interviewing-based patient counseling is proven to be an effective nonjudgmental patient-centered approach to enhance and reinforce health-related behavior [34–38]. Our motivational interview sessions usually last for 15 minutes and are repeated every 2 weeks to 3 months depending on patient needs, and they discontinue when patients have developed strong medication self-management skills along with sustained HIV-RNA undetectable values. Feasibility and effectiveness of the IMAP have been described elsewhere [19, 20, 39].

Strategies to improve retention and adherence should not only focus on the patient but also the patient’s environment. It is important to address social problems such as unemployment or isolation [40, 41] Those patients that are referred to participate in the IMAP are usually those who are nonadherers or those at a high risk due to psychosocioeconomic and clinical risk factors. Additional referral to specialized ancillary services such as social services or mental health services is provided by either the physician-nurse team or/and the pharmacists delivering the IMAP whenever needed. Furthermore, it is important that all HCPs collaborate and communicate with each other for the best treatment outcomes for the patients. Based on our results, gaps in care should be monitored in clinical practice as a quality indicator of care and should be considered as a criterion for including patients into medication adherence programs.

Standard of care in the SHCS consisted of the following actions [42]. Physicians and nurses give patients information

Table 3. Effect of the Intervention on 12-Month Treatment Gaps Comparing Different Methods to Adjust for Different Patient Populations at the Two Centers

Methods	N	OR (95% CI)	P	HR (95% CI)	P
Crude	726	0.47 (0.31–0.70)	<.001	0.51 (0.35–0.75)	.001
Adjusted for covariates	601	0.47 (0.28–0.78)	.004	0.46 (0.29–0.74)	.001
Adjusted for propensity score	601	0.48 (0.29–0.81)	.006	0.48 (0.30–0.76)	.002
Adjusted for propensity score + covariates	633	0.44 (0.29–0.68)	<.001	0.47 (0.29–0.75)	.002
IPTW weighted model	601	0.55 (0.32–0.96)	.03	0.52 (0.32–0.85)	.01
ISR weighted model	676	0.67 (0.38–1.18)	.17	0.77 (0.46–1.29)	.3

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; ISR, indirect standardization ratio; OR, odds ratio.

about HIV, treatment, and side effects. They also give information on the importance of medication adherence and the consequences of nonadherence without providing specific illustrative materials. Brochures and websites may be recommended to patients but not systematically. Patients get directions on the regimen and proper use of the treatment. They get a biannual feedback of their CD4 and viral load; medication adherence is reinforced, and potential causes for nonadherence are addressed by the physician and the nurse but without a systematic approach. Patients are encouraged to use of 7-day pill box if needed. A nurse assists patients with housing, unemployment, and financial and legal issues. Patients are told to contact the physician-nurse team if unexpected problems occur, and complex patients benefit from more frequent medical visits.

Many factors affecting retention in care have been addressed in the literature. Facilitating transportation and access to care, increasing the quality of patient-professional relationship, community-based accompaniment, decreasing health disparities, and stigma increase retention in care [43–45]. However, the impact on retention in care of IMAPs, which assess patients' complex and multiple needs, has rarely been investigated. Our results are consistent with another study showing that HIV medical case management, including medication adherence support, increased retention in care more than 4 times in comparison to facilities without case management [46].

Strengths and Limitations

This study is the first attempt to show the positive impact of a theory-based interprofessional medication adherence intervention on retention in care and clinical outcomes in a large cohort of PWH. The literature shows that program-level factors such as adherence support, motivational interviewing, and other ancillary services are likely to play an important role in patient retention, yet there is not enough published evidence on the effectiveness of medication adherence programs on retention in care [47, 48]. As shown in our results, gaps in care are common; they represent a silent concern that needs to be addressed. Continuous retention in care is a critical, yet rarely monitored, metrics of success [49].

Due to the lack of randomization, we cannot exclude the risk that there is a center-level effect, but we reduced this risk as much as possible. On the one hand, it is important to note that both ID centers work similarly in terms of medical activity. Medical interns attend medical school in Geneva or Lausanne, are trained in ID service in either center, and rotate every year. Second, several methodological approaches were used to adjust for differences in patient characteristics to attempt to balance the 2 centers as in a controlled trial. Based on the data collected through the SHCS, we tried to cover all crucial sociodemographic, clinical, and therapeutic variables. The stability of the intervention effect over all models, except the ISR-weighted model, suggests the

results are quite robust. The ISR-weighted models consider the intervention group to be the standard population rather than the entire population from both centers, so they answer a different question than the other models. However, we are more interested in the effect of the intervention when considering the SHCS population across all centers as the standard population. Third, we were able to show that baseline retention in care was similar in both groups before the start of the study, suggesting that it was not a difference in patients driving the observed difference in retention in the IG. Finally, the collected data represent the 2004–2012 time frame. We were not able to extend the comparison between both centers beyond this date because the standard of care has changed in 2013 in one center but not in the other one. Indeed, the control center introduced new operations to increase the retention in care to all their patients in 2013 such as automatic phone message recalls. Despite the fact that our data are anterior to 2013, they keep current validity per se to illustrate the impact of a medication adherence program on retention in care, especially because care delivery models have not changed in Switzerland since 2004. However, participant characteristics have changed since the era of universal treatment, increasing the need for medication adherence support as treatment starts earlier than ever, yet with less side effects.

CONCLUSIONS

There is an ongoing need for evidence-based interventions to increase retention in care. This study showed the potential of a theory-based medication adherence program for reducing gaps in follow up over 6- and 12-month periods among adult PWH. We suggest adapting and implementing this intervention in other settings to verify its effectiveness in increasing retention in care.

Acknowledgments

Author contributions. S. K., J.-J. P., M. C., and M. P. S. defined the research question and wrote the protocol. M. T. D.-L. provided the data of the control center. M. C. provided the data of the intervention center. M. P. S. and O. B. provided the adherence data. S. L. prepared the database. T. R. G. performed the statistical analysis. S. K., T. R. G., M. C., and M. P. S. wrote the manuscript, which was then reviewed by all authors.

Financial support. This study, financed within the framework of the Swiss HIV Cohort Study, was supported by the Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung (Grant No. 177499) and the Swiss HIV Cohort Research Foundation (Grant No. 768) (listed in <http://www.shcs.ch/180-health-care-providers>).

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Lohse N, Hansen AB, Gerstoft J, Obel N. Improved survival in HIV-infected persons: consequences and perspectives. *J Antimicrob Chemother* 2007; 60:461–3.
2. Taiwo B, Hicks C, Eron J. Unmet therapeutic needs in the new era of combination antiretroviral therapy for HIV-1. *J Antimicrob Chemother* 2010; 65:1100–7.

3. Giordano TP, Gifford AL, White AC Jr, et al. Retention in care: a challenge to survival with HIV infection. *Clin Infect Dis* **2007**; 44:1493–9.
4. Mugavero MJ, Lin HY, Willig JH, et al. Missed visits and mortality among patients establishing initial outpatient HIV treatment. *Clin Infect Dis* **2009**; 48:248–56.
5. Centers for Disease Control and Prevention. Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2017. *HIV Surveil Suppl Rep* **2019**; 1–74.
6. Gardner EM, McLees MP, Steiner JF, et al. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. *Clin Infect Dis* **2011**; 52:793–800.
7. Bangsberg DR, Perry S, Charlebois ED, et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* **2001**; 15:1181–3.
8. Hogg RS, Heath K, Bangsberg D, et al. Intermittent use of triple-combination therapy is predictive of mortality at baseline and after 1 year of follow-up. *AIDS* **2002**; 16:1051–8.
9. Crepaz N, Lyles CM, Wolitski RJ, et al.; HIV/AIDS Prevention Research Synthesis (PRS) Team. Do prevention interventions reduce HIV risk behaviours among people living with HIV? A meta-analytic review of controlled trials. *AIDS* **2006**; 20:143–57.
10. Yehia BR, French B, Fleishman JA, et al.; HIV Research Network. Retention in care is more strongly associated with viral suppression in HIV-infected patients with lower versus higher CD4 counts. *J Acquir Immune Defic Syndr* **2014**; 65:333–9.
11. Vrijens B, De Geest S, Hughes DA, et al.; ABC Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol* **2012**; 73:691–705.
12. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. *Annu Rev Pharmacol Toxicol* **2012**; 52:275–301.
13. Nachega JB, Uthman OA, del Rio C, et al. Addressing the Achilles' heel in the HIV care continuum for the success of a test-and-treat strategy to achieve an AIDS-free generation. *Clin Infect Dis* **2014**; 59 (Suppl 1):S21–7.
14. Mugavero MJ, Davila JA, Nevin CR, Giordano TP. From access to engagement: measuring retention in outpatient HIV clinical care. *AIDS Patient Care STDS* **2010**; 24:607–13.
15. Eaton EF, Saag MS, Mugavero M. Engagement in human immunodeficiency virus care: linkage, retention, and antiretroviral therapy adherence. *Infect Dis Clin North Am* **2014**; 28:355–69.
16. Glass TR, Bategay M, Cavassini M, et al.; Swiss HIV Cohort Study. Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* **2010**; 54:197–203.
17. Glass TR, De Geest S, Weber R, et al. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* **2006**; 41:385–92.
18. Perron NJ, Dao MD, Kossovsky MP, et al. Reduction of missed appointments at an urban primary care clinic: a randomised controlled study. *BMC Fam Pract* **2010**; 11:79.
19. Lelubre M, Kamal S, Genre N, et al. Interdisciplinary medication adherence program: the example of a university community pharmacy in Switzerland. *Biomed Res Int* **2015**; 2015:103546.
20. Krummenacher I, Cavassini M, Bugnon O, Schneider MP. An interdisciplinary HIV-adherence program combining motivational interviewing and electronic antiretroviral drug monitoring. *AIDS Care* **2011**; 23:550–61.
21. Krummenacher I, Cavassini M, Bugnon O, Schneider MP. Characteristics of HIV patients referred to a medication adherence program in Switzerland. *Int J Clin Pharm* **2012**; 34:426–31.
22. Krummenacher I, Cavassini M, Bugnon O, et al.; Swiss HIV Cohort Study. Antiretroviral adherence program in HIV patients: a feasibility study in the Swiss HIV Cohort Study. *Pharm World Sci* **2010**; 32:776–86.
23. Kamal S, Nulty P, Bugnon O, et al. Content analysis of antiretroviral adherence enhancing interview reports. *Patient Educ Couns* **2018**; 101:1676–82.
24. Keller SC, Yehia BR, Eberhart MG, Brady KA. Accuracy of definitions for linkage to care in persons living with HIV. *J Acquir Immune Defic Syndr* **2013**; 63:622–30.
25. World Health Organization. Retention in HIV programmes: defining the challenges and identifying solutions: meeting report, 13–15 September 2011. Geneva, Switzerland: World Health Organization. **2012**.
26. Sherer R, Stieglitz K, Narra J, et al. HIV multidisciplinary teams work: support services improve access to and retention in HIV primary care. *AIDS Care* **2002**; 14 Suppl 1:S31–44.
27. Lo W, MacGovern T, Bradford J. Association of ancillary services with primary care utilization and retention for patients with HIV/AIDS. *AIDS Care* **2002**; 14 (Suppl 1):S45–57.
28. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* **1983**; 70:41–55.
29. Rubin DB, Thomas N. Combining propensity score matching with additional adjustments for prognostic covariates. *J Am Stat Assoc* **2000**; 95:573–85.
30. Sato T, Matsuyama Y. Marginal structural models as a tool for standardization. *Epidemiology* **2003**; 14:680–6.
31. Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* **2000**; 11:550–60.
32. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med* **2012**; 156:817–33.
33. Higa DH, Marks G, Crepaz N, et al. Interventions to improve retention in HIV primary care: a systematic review of U.S. studies. *Curr HIV/AIDS Rep* **2012**; 9:313–25.
34. Hettema J, Steele J, Miller WR. Motivational interviewing. *Annu Rev Clin Psychol* **2005**; 1:91–111.
35. Burke BL, Arkowitz H, Menchola M. The efficacy of motivational interviewing: a meta-analysis of controlled clinical trials. *J Consult Clin Psychol* **2003**; 71:843–61.
36. DiIorio C, McCarty F, Resnicow K, et al. Using motivational interviewing to promote adherence to antiretroviral medications: a randomized controlled study. *AIDS Care* **2008**; 20:273–83.
37. Hill S, Kavookjian J. Motivational interviewing as a behavioral intervention to increase HAART adherence in patients who are HIV-positive: a systematic review of the literature. *AIDS Care* **2012**; 24:583–92.
38. Miller WR, Rollnick S. *Motivational Interviewing: Helping People Change*. 3rd ed. New York: Guilford Press; **2012**.
39. Perraudin C, Locca JF, Rossier C, et al. Implementation of an interprofessional medication adherence program for chronic patients in community pharmacies: how much does it cost for the provider? *BMC Health Serv Res* **2019**; 19:15.
40. Andersen M, Hockman E, Smereck G, et al. Retaining women in HIV medical care. *J Assoc Nurses AIDS Care* **2007**; 18:33–41.
41. Kushel MB, Colfax G, Ragland K, et al. Case management is associated with improved antiretroviral adherence and CD4+ cell counts in homeless and marginally housed individuals with HIV infection. *Clin Infect Dis* **2006**; 43:234–42.
42. de Bruin M, Viechtbauer W, Hospers HJ, et al. Standard care quality determines treatment outcomes in control groups of HAART-adherence intervention studies: implications for the interpretation and comparison of intervention effects. *Health Psychol* **2009**; 28:668–74.
43. Anderson AN, Higgins CM, Haardörfer R, et al. Disparities in retention in care among adults living with HIV/AIDS: a systematic review. *AIDS Behav* **2020**; 24:985–97.
44. Cluver L, Pantelic M, Toska E, et al. STACKing the odds for adolescent survival: health service factors associated with full retention in care and adherence amongst adolescents living with HIV in South Africa. *J Int AIDS Soc* **2018**; 21:e25176.
45. Franke MF, Kaigamba F, Socci AR, et al. Improved retention associated with community-based accompaniment for antiretroviral therapy delivery in rural Rwanda. *Clin Infect Dis* **2013**; 56:1319–26.
46. Willis S, Castel AD, Ahmed T, et al. Linkage, engagement, and viral suppression rates among HIV-infected persons receiving care at medical case management programs in Washington, DC. *J Acquir Immune Defic Syndr* **2013**; 64 (Suppl 1):S33–41.
47. Geng EH, Nash D, Kambugu A, et al. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. *Curr HIV/AIDS Rep* **2010**; 7:234–44.
48. Shaw S, Amico KR. Antiretroviral therapy adherence enhancing interventions for adolescents and young adults 13–24 years of age: a review of the evidence base. *J Acquir Immune Defic Syndr* **2016**; 72:387–99.
49. Colasanti J, Kelly J, Pennisi E, et al. Continuous retention and viral suppression provide further insights into the HIV care continuum compared to the cross-sectional HIV care cascade. *Clin Infect Dis* **2016**; 62:648–54.