Kantonsspital Aarau

Research Council KantonsspitalAarau

Scientific Project Submission

Date: 29th August 2012

1. Applicant (first name, last name): a) Andrea Bregenzer
b) Christoph Fux

Degree(s): A.B. Medical doctor (MD)
C.F. MD, PD

Institution name and address:
Klinik für Infektiologie und Spitalhygiene
Kantonsspital Aarau
Tellstrasse
5000 Aarau

2. Title of proposal:
Management of hepatitis C in drug substitution programs – Kanton Aargau

3.Total amount requested: 160'000 CHF
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4. Scientific abstract: Please do not exceed 1 page.

Hepatitis C in drug substitution programs – canton Aargau

Background: In Switzerland, intravenous drug use (IDU) accounts for 80% of newly acquired hepatitis C virus (HCV) infections; 60-80% of patients in drug substitution programs are HCV infected. Hepatitis C can be cured and early treatment has the potential to interrupt the transmission chain and reduce morbidity/mortality due to decompensated liver cirrhosis and hepatocellular carcinoma. Treatment adherence, side effects and treatment response do not differ between IDUs and non-IDUs, and drug substitution programs are an ideal setting for directly observed therapy (DOT). Nevertheless, patients in drug substitution programs are often insufficiently screened and treated. HCV rapid testing with capillary blood ("fingerstick") and non-invasive measurement of liver fibrosis with Fibroscan® can overcome barriers to diagnosis. With telaprevir and boceprevir, HCV genotype 1 can now be treated similarily successful as HCV genotypes 2 and 3.

Aim: 1) To improve the management of HCV infection in drug substitution programs of the Kanton Aargau including screening for HCV and its complications (cirrhosis, hepatocellular cancer), prevention of coinfections (hepatitis A and B) and treatment up-take according to the recommendations of the Swiss Society of Addiction Medicine.

2) To publish internationally lacking data on the infectious diseases management of drug substitution patients in a decentralized setting as found in the Kanton Aargau.
3) To improve cooperation of professionals caring for drug substitution patients including health administration and clinical care providers (general practitioners as well as the cantonal hospitals of Aarau and Baden).

Methodology:
The **first step** will be a **cross-sectional study** investigating the current state of HCV management. For all 800 patients cared for in a drug substitution program in the Kanton Aargau, the physician providing substitution treatment will be contacted by the Kantonsarzt, Dr. Roth, providing a questionnaire and free fingerstick blood test kits for HIV and HCV. The treating physician will be asked to fill in the questionnaire and perform the capillary tests at the next patient's visit. In addition, liver fibrosis will be measured by a member of the study team with Fibroscan®. This will be organized either as coordinated measurements of all substitution patients in the respective general practice or substitution pharmacy or on an individual basis in Aarau or Baden. Major outcome measures will be HCV and HIV screening rate, the prevalence of HCV and HIV infection and the immunisation status against hepatitis A and B. (Patients without livelong immunity against hepatitis B will be offered to participate in a randomised hepatitis B vaccination study.) For HCV, the time of diagnosis, the spontaneous clearance rate, HCV genotype distribution, the prevalence of liver fibrosis and cirrhosis, treatment uptake, the delay between HCV infection, diagnosis and treatment, barriers to treatment and the success rate in mono- and HIV-co-infected patients, will be assessed.
All suitable data will be included in the newly funded Swiss cohort of patients in drug substitution programs enabling the Kanton Aargau to significantly contribute to research in this field.
The **second step** will be a longitudinal follow-up (**cohort study**) addressing the incidence of HCV new and re-infections, treatment uptake, treatment complications and outcome, predictors for HCV treatment response as well as the incidence of and predictors for HCV related complications such as liver cirrhosis or hepatocellular carcinoma. As biyearly Fibroscan® follow-up irrespective of HCV status will be offered to all drug substitution patients, both infectious and non-infectious liver diseases in drug addicts will be captured.
Treatment indication for HCV, treatment modalities and follow-up will be according to current national and international guidelines and will not be influenced by our study.

The establishment of a **cantonal interdisciplinary HCV treatment network** including family doctors, infectious diseases specialists, gastroenterologists, psychiatrists, drug addiction specialists, neurologists, dermatologists and social workers is a key goal of the study.

5a. Biographical sketch: Andrea Bregenzer
Personal data:
Name: Andrea Bregenzer (née Witteck)
Date of birth: 30th March 1977
Place of birth: Halle/Saale, Germany
Nationality: German
Living in Switzerland: since 2002
Marital status: married
Children: 1 daughter (2011)

Training and qualifications:
School: 1996 Abitur at the Eleonorenschule (Gymnasium), Darmstadt(Germany)
University: 1996-2002 Study of Human Medicine at the Johannes Gutenberg-University, Mainz (Germany),

Since 2011 distance learning course MSc Epidemiology at the London School of Hygiene and Tropical Medicine (LSHTM) in collaboration with the University of London
Doctoral thesis: 2002 "Regulation of the expression of the human inducible NO synthase (iNOS) by small G proteins" (Supervisors: Prof. Hartmut Kleinert and Prof. Ulrich Förstermann, Department of Pharmacology of the Johannes Gutenberg-University, Mainz (Germany))
Professionalqualifications:
2008 Specialist in Internal Medicine (FMH, Swiss MedicalAssociation)
2010 Infectious Diseases Specialist (FMH, Swiss MedicalAssociation)

6a. Home address: Andrea Bregenzer, Entfelderstrasse 56, 5000 Aarau

7a. Date and place of birth: 30th March 1977 in Halle/Saale, Germany

8a. Research and/or professional experience:
Positions (in reverse chronological order):
since 01.04.2011 Senior physician in the Department of Infectious Diseases, Cantonal Hospital Aarau (Aargau, Switzerland) (50%)
since 01.10.2010 Senior physician in the Department of Infectious Diseases, Cantonal Hospital St. Gallen (St. Gallen, Switzerland)(100% until 31.03.2011, 50% since 01.04.2011, 30% since 01.10.2011)
01.03.2007-30.9.2010 Resident physician in the Department of Infectious Diseases, Cantonal Hospital St. Gallen (St. Gallen, Switzerland)
01.11.2004-28.02.2007 Resident physician in the Department of Internal Medicine, Cantonal Hospital Aarau (Aargau, Switzerland)
01.01.2004 – 31.10.2004 Resident physician in the Department of Internal Medicine, Cantonal Hospital Nidwalden in Stans (Nidwalden, Switzerland)
01.11.2002 – 31.12.2003 Resident physician in the Department of Internal Medicine, Hospital Menziken (Aargau, Switzerland)

Publications during the past three years (in chronological order):
Witteck A, Yerly S, Vernazza P. Unusually high HIV infectiousness in an HIV-, HCV- and HSV-2-coinfected heterosexual man. Swiss Med Wkly 2009;139(13-14):207-209
Rotger M, Bayard C, Taffé P, Martinez R, Cavassini M, Bernasconi E, Battegay M, Hirschel B, FurrerH, **Witteck A**, Weber R, Ledergerber B, Telenti A, Tarr PE; Swiss HIV Cohort Study. Contribution ofgenome-wide significant single-nucleotide polymorophisms and antiretroviral therapy to dyslipidemiain HIV-infected individuals: a longitudinal study. CircCardiovasc Gent 2009;2(6):621-628
Rauch A, Kutalik Z, Descombes P, Cai T, Di Lulio J, Müller T, Bochud M, Battegay M, BernasconiE, Borovicka J, Colombo S, Cerny A, Dufour JF, Furrer H, Günthard HF, Heim M, Hirschel B,Malinverni R, Moradpour D, Müllhaupt B, **Witteck A**, Beckmann JS, Berg T, Bergmann S, Negro F, Telenti A, Bochud PY; Swiss Hepatitis C and HIV Cohort Studies. Genetic variation in IL28B isassociated with chronic hepatitis C and treatment failure: a genome-wide association study.Gastroenterology 2010;138(4):1338-1345
Witteck A, Schmid P. Hepatitis C–Update 2010. Swiss Medical Forum 2010;10(42):729-736
Bluzaite I, **Witteck** A, Roelli H, Rickli H. Diagnostic ergometry in an HIV-positive patient with effortdyspnea. Cardiovascular Medicine 2010;13(11):342-345
Kenfak-Foguena A, Schöni-Affolter F, Bürgisser P, **Witteck A**, Darling KE, Kovari H, Kaiser L,Evison JM, Elzi L, Gurter-De La Fuente V, Jost J, Moradpour D, Abravanel F, Izpopet J, Cavassini M; Data Center of the Swiss HIV Cohort Study, Lausanne, Switzerland. Hepatitis E virusseroprevalence and chronic infections in patients with HIV, Switzerland.Emerg Infect Dis2011;17(6):1074-1078
Witteck A, Schmid P, Hensel-Koch K, Thurnheer MC, Bruggmann P, Vernazza P; Swiss Hepatitis Cand HIV Cohort Studies. Management of hepatitis C virus (HCV) infection in drug substitutionprograms. Swiss Med Wkly 2011;141:w13193

Witteck A, Rettenmund G, Schlegel M. MRSA admission screening in a low prevalence setting -much ado about nothing? Swiss Med Wkly 2011;141:w13217
Pillai SK, Abdel-Mohsen M, Guatelli J, Skasko M, Monto A, Fujimoto K, Yukl S, Greene WC, Kovari H, Rauch A, Fellay J, Battegay M, Hirschel B, **Witteck A**, Bernasconi E, Ledergerber B, Günthard HF, Wong JK; Swiss HIV Cohort Study.Role of retroviral restriction factors in the interferon-α-mediated suppression of HIV-1 in vivo. ProcNatlAcadSci USA 2012;109(8):3035-40
Kohler P, **Bregenzer-Witteck A**, Rettenmund G, Otterbech S, Schlegel M. MRSA decolonization: success rate, risk factors for failure and optimal duration of follow-up. Infection. 2012 Jul 11. [Epub ahead of print]
Wandeler G, Gsponer T, **Bregenzer A**, Günthard HF, Clerc O, Calmy A, Stöckle M, Bernasconi E, Furrer H, Rauch A; the Swiss HIV Cohort Study. Hepatitis C Virus Infections in the Swiss HIV Cohort Study: A Rapidly Evolving Epidemic. Clin Infect Dis. 2012 Aug 14. [Epub ahead of print]

5b. Biographical sketch: Christoph Fux
Personal data:
Name: Christoph Andreas Fux
Date of birth: 30th January 1968
Place of birth: Zürich ZH
Nationality: Swiss
Marital status: married
Children: Jonas (*1997), Julian (*1999), Severin (*2004)

Training and qualifications:
School: 1987 Maturität Typ B, Gymnasium Kirchenfeld Bern
University: 1988-94 Study of Human Medicine at University of Bern, Switzerland
1992/97 American Medical Licensing Exam (ECFMG)
Doctoral thesis: 1994
Professionalqualifications:
2001 Board affiliation in Internal Medicine (FMH)
2008 Board affiliation in Infectious Diseases (FMH)

6b. Home address: Christoph Fux, Gebhartstrasse 17, 3097 Liebefeld

7b. Research and/or professional experience:
Positions (in reverse chronological order):
since 1.1.2011 Head Clinic for Infectious Diseases and Hospital Hygiene, Kantonsspital Aarau
2000-2010 Resident, senior resident and ad interim Head of Outpatient Department Clinic for Infectious Diseases and Hospital Hygiene, University Hospital Insel, Bern
1995-2000 Residency in Anesthesiology (Kantonsspital Luzern), Intensive Care (Kantonsspital Luzern, Inselspital Bern) and Internal Medicine (Zieglerspital Bern, Inselspital Bern)

Publications during the past three years (in chronological order):
A comparison of measured and estimated glomerular filtration rate in successfully treated HIV-patients with preserved renal function. Vrouenraets SM, **Fux CA**, Wit FW, Garcia EF, Brinkman K, Hoek FJ, van Straalen JP, Furrer H, Krediet RT, Reiss P; Prepare Study Group. Clin Nephrol. 2012 Apr;77(4):311-20.
Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir. Young J, Schäfer J, **Fux CA**, Furrer H, Bernasconi E, Vernazza P,

Calmy A, Cavassini M, Weber R, Battegay M, Bucher HC; Swiss HIV Cohort Study. AIDS. 2012 Mar 13;26(5):567-75.

H1N1 outbreak in a Swiss military boot camp--observations and suggestions. Jeger V, Dünki A, Germann M, **Fux CA**, Faas A, Exadaktylos AK, Stettbacher A. Swiss Med Wkly. 2011 Nov 30;141:w13307

Persistent decline in estimated but not measured glomerular filtration rate on tenofovir may reflect tubular rather than glomerular toxicity. Vrouenraets SM, **Fux CA**, Wit FW, Garcia EF, Furrer H, Brinkman K, Hoek FJ, Abeling NG, Krediet RT, Reiss P; Prepare Study Group. AIDS. 2011 Nov 13;25(17):2149-55.

High specificity of line-immunoassay based algorithms for recent HIV-1 infection independent of viral subtype and stage of disease. Schüpbach J, Bisset LR, Regenass S, Bürgisser P, Gorgievski M, Steffen I, Andreutti C, Martinetti G, Shah C, Yerly S, Klimkait T, Gebhardt M, Schöni-Affolter F, Rickenbach M; Swiss HIV Cohort Study, Barth J, Battegay M, Bernascon E, Böni J, Bucher HC, Bürgisser P, Burton-Jeangros C, Calmy A, Cavassini M, Dubs R, Egger M, Elzi L, Fehr J, Fischer M, Flepp M, Francioli P, Furrer H, **Fux CA**, Gorgievski M, Günthard H, Hasse B, Hirsch HH, Hirschel B, Hösli I, Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Müller N, Nadal D, Pantaleo G, Rauch A, Regenass S, Rickenbach M, Rudin C, Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Telenti A, Trkola A, Vernazza P, von Wyl V, Weber R, Yerly S. BMC Infect Dis. 2011 Sep 26;11:254.

Efficacy, tolerability and risk factors for virological failure of darunavir-based therapy for treatment-experienced HIV-infected patients: the Swiss HIV Cohort Study. Young J, Scherrer AU, Günthard HF, Opravil M, Yerly S, Böni J, Rickenbach M, **Fux CA**, Cavassini M, Bernasconi E, Vernazza P, Hirschel B, Battegay M, Bucher HC; Swiss HIV Cohort Study. HIV Med. 2011 May;12(5):299-307. doi: 10.1111/j.1468-1293.2010.00885.x. Epub 2010 Oct 18.

Is lower serum 25-hydroxy vitamin D associated with efavirenz or the non-nucleoside reverse transcriptase inhibitor class? **Fux CA**, Baumann S, Furrer H, Mueller NJ. AIDS. 2011 Mar 27;25(6):876-8.

Replicative phenotyping adds value to genotypic resistance testing in heavily pre-treated HIV-infected individuals--the Swiss HIV Cohort Study. Fehr J, Glass TR, Louvel S, Hamy F, Hirsch HH, von Wyl V, Böni J, Yerly S, Bürgisser P, Cavassini M, **Fux CA**, Hirschel B, Vernazza P, Martinetti G, Bernasconi E, Günthard HF, Battegay M, Bucher HC, Klimkait T; Swiss HIV Cohort Study. J Transl Med. 2011 Jan 21;9:14.

Dialysis and renal transplantation in HIV-infected patients: a European survey. Trullas JC, Mocroft A, Cofan F, Tourret J, Moreno A, Bagnis CI, **Fux CA**, Katlama C, Reiss P, Lundgren J, Gatell JM, Kirk O, Miró JM; EuroSIDA Investigators. J Acquir Immune Defic Syndr. 2010 Dec 15;55(5):582-9.

High prevalence of severe vitamin D deficiency in combined antiretroviral therapy-naive and successfully treated Swiss HIV patients. Mueller NJ, **Fux CA**, Ledergerber B, Elzi L, Schmid P, Dang T, Magenta L, Calmy A, Vergopoulos A, Bischoff-Ferrari HA; Swiss HIV Cohort Study. AIDS. 2010 May 15;24(8):1127-34.

Prior therapy influences the efficacy of lamivudine monotherapy in patients with lamivudine-resistant HIV-1 infection. Opravil M, Klimkait T, Louvel S, Wolf E, Battegay M, **Fux CA**, Bernasconi E, Vogel M, Speck R, Weber R; Swiss HIV Cohort Study. J Acquir Immune Defic Syndr. 2010 May 1;54(1):51-8.

Implementation of raltegravir in routine clinical practice: selection criteria for choosing this drug, virologic response rates, and characteristics of failures. Scherrer AU, von Wyl V, **Fux CA**, Opravil M, Bucher HC, Fayet A, Decosterd LA, Hirschel B, Khanlari B, Yerly S, Klimkait T, Furrer H, Ledergerber B, Günthard HF; Swiss HIV Cohort Study. J Acquir Immune Defic Syndr. 2010 Apr 1;53(4):464-71.

Low bone mineral density, renal dysfunction, and fracture risk in HIV infection: a cross-sectional study. Calmy A, **Fux CA**, Norris R, Vallier N, Delhumeau C, Samaras K, Hesse K, Hirschel B, Cooper DA, Carr A. J Infect Dis. 2009 Dec 1;200(11):1746-54.

Discontinuation of enfuvirtide in heavily pretreated HIV-infected individuals. Elzi L, Kaufmann G, Weber R, **Fux CA**, Cavassini M, Hirschel B, Vernazza P, Bernasconi E, Battegay M; Swiss HIV Cohort Study. HIV Clin Trials. 2009 Jul-Aug;10(4):207-14.
Incidence and outcome of progressive multifocal leukoencephalopathy over 20 years of the Swiss HIV Cohort Study. Khanna N, Elzi L, Mueller NJ, Garzoni C, Cavassini M, **Fux CA**, Vernazza P, Bernasconi E, Battegay M, Hirsch HH; Swiss HIV Cohort Study. Clin Infect Dis. 2009 May 15;48(10):1459-66.
JC virus-specific immune responses in human immunodeficiency virus type 1 patients with progressive multifocal leukoencephalopathy. Khanna N, Wolbers M, Mueller NJ, Garzoni C, Du Pasquier RA, **Fux CA**, Vernazza P, Bernasconi E, Viscidi R, Battegay M, Hirsch HH; Swiss HIV Cohort Study. J Virol. 2009 May;83(9):4404-11.
Syphilitic myelitis: rare, nonspecific, but treatable. Chilver-Stainer L, Fischer U, Hauf M, **Fux CA**, Sturzenegger M. Neurology. 2009 Feb 17;72(7):673-5.
Virological and immunological responses to efavirenz or boosted lopinavir as first-line therapy for patients with HIV. Young J, Bucher HC, Guenthard HF, Rickenbach M, **Fux CA**, Hirschel B, Cavassini M, Vernazza P, Bernasconi E, Battegay M; Swiss HIV Cohort Study. Antivir Ther. 2009;14(6):771-9.
Holiday souvenirs from the Mediterranean: three instructive cases of visceral leishmaniasis. Buonomano R, Brinkmann F, Leupin N, Boscacci R, Zimmermann A, Müller N, **Fux CA**. Scand J Infect Dis. 2009;41(10):777-81.
Elevated triglycerides and risk of myocardial infarction in HIV-positive persons. Worm SW, Kamara DA, Reiss P, Kirk O, El-Sadr W, **Fux C**, Fontas E, Phillips A, D'Arminio Monforte A, De Wit S, Petoumenos K, Friis-Mller N, Mercie P, Lundgren JD, Sabin C. AIDS. 2011 Jul 31;25(12):1497-504.
Outcomes of patients on dual-boosted PI regimens: experience of the Swiss HIV cohort study. Osih RB, Taffé P, Rickenbach M, Gayet-Ageron A, Elzi L, **Fux C**, Opravil M, Bernasconi E, Schmid P, Günthard HF, Cavassini M; Swiss HIV Cohort Study. AIDS Res Hum Retroviruses. 2010 Nov;26(11):1239-46.
Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. Gutmann C, Cusini A, Günthard HF, **Fux C**, Hirschel B, Decosterd LA, Cavassini M, Yerly S, Vernazza PL; Swiss HIV Cohort Study (SHCS). AIDS. 2010 Sep 24;24(15):2347-54.
Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. Marzolini C, Elzi L, Gibbons S, Weber R, **Fux C**, Furrer H, Chave JP, Cavassini M, Bernasconi E, Calmy A, Vernazza P, Khoo S, Ledergerber B, Back D, Battegay M; Swiss HIV Cohort Study. Antivir Ther. 2010;15(3):413-23.
Randomized trial of a computerized coronary heart disease risk assessment tool in HIV-infected patients receiving combination antiretroviral therapy. Bucher HC, Rickenbach M, Young J, Glass TR, Vallet Y, Bernasconi E, Cavassini M, **Fux C**, Schiffer V, Vernazza P, Weber R, Battegay M; Swiss HIV Cohort Study. Antivir Ther. 2010;15(1):31-40.
Donor-to-host transmission of Candida glabrata to both recipients of corneal transplants from the same donor. Tappeiner C, Goldblum D, Zimmerli S, **Fux C**, Frueh BE. Cornea. 2009 Feb;28(2):228-30.

9. List ALL financial support (pending or current), regardless of source.
None.

10. Does the research involve human subjects?
Yes: X No:

Should this application result in the financing of a project, the relevant ethical approval/s must be forwarded to the Research Council as soon as possible.

Please note: No payments will be transferred without the appropriate approval/s.

11.Budget

A detailed budget must be provided on the following pages (please complete all parts of the forms).

The budget period (time) during which the sum will be spent must be clearly stated and justified where indicated.

Total budget period (in months): 36

Budget category	Role in project	% Effort on project	Salary request *
Infectious diseases specialist (senior physician) Andrea Bregenzer	▪ submission of the projects to the ethics committee ▪ coordination of interdisciplinary collaboration ▪ consultations for Aarau-based assessments including Fibroscan® examinations ▪ writing of patient-specific diagnostic (e.g. liver biopsy), treatment (HCV) and vaccination (HAV, HBV) recommendations based on information from the questionnaire and the general practicioners ▪ provision of phone support and regular feedback for GPs ▪ analysis of the questionnaire ▪ publication of the cross-sectional study in a peer-reviewed journal ▪ writing of study protocol for the hepatitis B vaccination study ▪ Writing of questionnaire/flow sheet for longitudinal follow-up based on the cross-sectional data	3 years à 20%	CHF 90'000
Study nurse To be determined	▪ Electronic data collection, completion and cleaning ▪ organization of Aarau-based examinations (Fibroscan®, lab tests)	3 years à 10%	CHF 30'000
Other costs	Reimbursement for the treating physicians filling in the 800 questionnaires (50 CHF for each questionnaire)		CHF 40'000
Total costs			CHF 160'000

* Incl. socialcharges, fringebenefits

additional funding	

• Mobile Fibroscan® 402 (Echosens) for non-invasive measurement of liver fibrosis: 44’770 CHF • 800 OraQuick®-HCV-antibody rapid tests of capillary blood à 25 CHF: 20’000 CHF • 800 Determine®-HIV-antigen/antibody combo rapid tests of capillary blood à 10 CHF: 8’000 CHF	Grant submission to pharmaceutical companies Roche, MSD, Janssen for CHF 72’770 pending
• ABX Micros ES 60 (Axon Lab) for complete blood count from capillary blood: 14’870 CHF	Planned infrastructural grant submission inhouse together with Prof. A. Huber for CHF 14’870

12.Research plan:

This section should be completed by the principal investigator (applicant). The research plan (a to g) must not exceed 3 pages. The narrative sections should be typewritten, single spaced, in type no smaller than 12-point font. References and letters of collaboration are not included in the 3-page limit. Applications with research plans exceeding 3 pages will not be considered for review.

a. **Title**
b. **Background / current status of research in the field**
c. **Past contribution of the applicant in the field**
d. **Specific aims and methods for the period of requested support**
e. **Preliminarydata**
f. **Significance of this work to the field**
g. **Facilitiesavailable**
h. **References (nopagelimit)**

Hepatitis C in drug substitution programs – canton Aargau

Background / current status of research in the field

In Switzerland, intravenous drug use (IDU) accounts for 80% of newly acquired hepatitis C virus (HCV) infections[1]. 60-80% of patients in drug substitution programs are HCV infected[2,3]. 70% of infected develop chronic hepatitis C (=persistent virus replication), which without treatment results in liver cirrhosis in 10-20% after 20 years. Of the cirrhotic patients, yearly 1-3% develop hepatocellular carcinoma[4]. Hepatitis C can be cured and early treatment has the potential to interrupt the transmission chain and reduce morbidity/mortality due to decompensated liver cirrhosis and hepatocellular carcinoma[4]. Once decompensated liver cirrhosis has developed, liver transplantation remains the only treatment option. HCV treatment success rates with current standard treatment (pegylated interferon-α + ribavirin for (16-)24-48(-72) weeks) are 40-50% for genotype 1, 60-70% for genotype 4 and 80% for genotype 2 and 3 in HCV mono-infected patients[4]. Treatment adherence, side effects and treatment response do not differ between IDUs and non-IDUs[5-7], and drug substitution programs are an ideal setting for directly observed therapy (DOT)[8]. Nevertheless, patients in drug substitution programs are often insufficiently screened[9,10] and treated[2,3,11,12]. HCV rapid testing with capillary ("fingerstick") blood[13] and non-invasive measurement of liver fibrosis[14,15] with Fibroscan® can overcome barriers to diagnosis. In Switzerland, ~50% of chronic hepatitis C infections are due to genotype 1[16]. With telaprevir and boceprevir, treatment-naïve HCV genotype 1 patients can now successfully be treated in ~70 and in ~50% treatment can be shortened. In case of unsuccessful prior standard treatment, retreatment including telaprevir or boceprevir has shown success rates of >80%, ~50% and ~30% for prior relapsers, partial and null responders, respectively[17].

Past contribution of the applicant in the field: In December 2009, Andrea Bregenzer conducted a cross sectional study on the management of HCV infection in three opioid substitution programs in St. Gallen (125 methadone and 71 heroin recipients). Results were compared with the heroin substitution program in Bern led by the clinic for infectious diseases of the University hospital in Bern under contribution of Christoph Fux (202 patients) and data of the Swiss Hepatitic C and Swiss HIV Cohort Studies (SCCS/SHCS). This resulted in a publication in Swiss Medical Weekly 2011[3].
In 2010, Andrea Bregenzer has written a review on hepatitis C for the Swiss Medical Forum entitled "Hepatitis C–Update 2010"[4].
Andrea Bregenzer has been and is still involved in several projects of the SHCS concerning hepatitis C infection. Furthermore, she is a foundation member of the Swiss Association for the Medical Management in Substance Users (SAMMSU) (founded on the 19th May 2011 in Zurich) which currently is establishing a Swiss cohort in drug substitution programs with anonymized data collection in a nationwide data base.
Christoph Fux is member of the SHCS scientific Board and has contributed to many studies in the field of HIV with a focus on metabolism, in particular renal and bone toxicity. He has received funding from SNF/SHCS as well as unrestricted (Abbott, BMS) and study-specific (Gilead) study grants.

Specific aims and methods for the period of requested support

Aim: To assess and improve the management of HCV infection in drug substitution programs of the Kanton Aargau including prevention, screening and treatment up-take according to the recommendations of the Swiss Society of Addiction Medicine[18]. This includes yearly HCV and HIV screening in those HCV and HIV negative, respectively; determination of HCV RNA if HCV positive and HCV genotype if HCV RNA positive; vaccination against hepatitis A and B in the absence of immunity (to prevent fatal liver

decompensation from acute hepatitis A and B in patients with pre-existing hepatitis C[4]); in case of liver cirrhosis screening for hepatocellular carcinoma every 6 months (sonography + α-fetoprotein) and biannual screening for oesophagus varices by gastroscopy; rapid evaluation by a specialist in case of acute hepatitis C (better treatment outcome than chronic hepatitis C irrespective of genotype[19]); HCV treatment evaluation, if RNA positive and HIV treatment irrespective of CD4 count in HIV-HCV-co-infected with chronic hepatitis C[20].

Methodology: The first step will be a **cross-sectional study** (start January 2013: expected approval of telaprevir/boceprevir for HIV-HCV-co-infected patients[21]) investigating the current state of HCV management. Submission of the study protocol to the ethics committee is planned for the 27.09.12, publication in a peer-reviewed journal in 2014. The study includes all 800 patients cared for in a drug substitution program in the Kanton Aargau. All physicians providing substitution treatment will be contacted by Dr. M. Roth, the Kantonsarzt of the Kanton Aargau, providing them with a questionnaire and free fingerstick HCV and HIV screening tests. The treating physicians will inform their patients at their next visit, seek informed consent and if obtained fill in the questionnaire (appendix) and perform both the serologic tests. Only then, the identity of study participants will be communicated to the study team. In parallel, liver fibrosis will be measured by Fibroscan® by a member of the study team in the private practice or the hospital of Aarau or Baden. Major outcome measures will be HCV and HIV screening rate and prevalence; the rate of spontaneous HCV clearance; delay between HCV infection, diagnosis and treatment; barriers to treatment; treatment success rate in mono- and HIV-co-infected patients; HCV genotype distribution; prevalence of liver fibrosis and cirrhosis; immunisation against hepatitis A and B.
Implementation of the recommendations of the Swiss Society of Addiction Medicine. Based on the questionnaire, the study team will give individual recommendations for further diagnostic workup and treatment/vaccination. Treatment indicationd, treatment modalities and follow-up will follow current national and international guidelines and will not be influenced by our study. In the event of HCV treatment, DOT (directly observed therapy) can be offered by the physician providing substitution treatment. The HCV treatment can be performed by the private physician and/or an infectious diseases specialist or gastroenterologist at the disrection of the patient and his treating physician. For study purposes, a minimum of 4 consultations will be held a study center (Kantonsspital Baden or Aarau): week 0 (start), 4 (rapid virological response?, ribavirin serum level), 12 (early virological response?, treatment failure?) and 6 months after treatment (sustained virological response?). In between, the physician providing substitution treatment is supported by phone helpline, a strategy that has proven equally successful as HCV treatments in specialized centres[22,23]. For optimal treatment, a **cantonal interdisciplinary HCV treatment network** (including family doctors, infectious diseases specialists, gastroenterologists, psychiatrists, drug addiction specialists, neurologists, dermatologists, social workers, etc.) will be established. Biannual Fibroscan® follow-up irrespective of HCV status will be offered, thus capturing both infectious and non-infectious liver diseases in drug addicts. Patients without livelong immunity against hepatitis B will be offered to participate in a randomised hepatitis B vaccination study comparing 3x 20ug i.c., 3x 20ug i.m. (standard) and 3x 40ug i.m.[24,25,26] month 0, 1 and 6 (combination vaccination in case of non-immunity against hepatitis A). A separate study protocol will be developed and submitted to the ethics committee.
The second step is a longitudinal follow-up (**cohort study**) addressing the incidence of HCV new and re-infections, predictors for HCV treatment response as well as incidence of and predictors for HCV related complications (e.g. liver cirrhosis, hepatocellular carcinoma). For all patients who provided specific informed consent, HCV-related anonymized data will be included in the new Swiss cohort in drug substitution programs.

Preliminary data: In 2009, about 17.000 patients were cared for in drug substitution programs throughout Switzerland, 800 of whom in the Kanton Aargau (BAG). In contrast to other cantons, care for the majority is not concentrated on a few centralized institutions, but distributed among 25-30 general practitioners. As there is no published data on the quality of HCV management in decentralized settings, the Aargau experience will be of broader interest.
For fingerstick blood, the HCV antibody rapid test (OraQuick®) has a sensitivity of 99.7% and a specificity of 99.9%[13] (test result within 30 minutes) and the HIV antigen/antibody combo rapid test (Determine®) has a sensitivity of 100% and a specificity of 99.8% (test result within 20 minutes).
The non-invasive, quantitative measurement of liver fibrosis with Fibroscan® is painless, reproducible and well accepted by patients. It takes only about 5 minutes, can be repeated in short intervals to monitor non-linear fibrosis progression and is well suited for significant fibrosis (AUROC 0.84) and cirrhosis (AUROC 0.94)[27]. Limitations are overweight (technical), acute hepatitis (false positive) and pregnancy/pace-maker/ascites (contraindications).
With 10 ul of capillary blood, the ABX Micros ES 60 from Axon Lab provides a complete blood count within less than 5 minutes, which is substantially less than the current waiting time for the results (up to 1 hour) in the central laboratory. To monitor side effects, this examination is often necessary on a weekly basis during HCV treatment.

Significance of this work to the field: Several studies have shown that participants of drug substitution programs are underdiagnosed[9,10] and undertreated[2,3,11,12] with respect to hepatitis C, although they are the main source of new infections[1]. The situation in the Kanton Aargau is unknown, but of special interest because – in contrast to other cantons – family doctors rather than one specialized institution provide substitution treatment. Therefore, the current project is welcomed and actively supported by the Kantonsarzt (co-author of the study). Enhanced diagnosis and timely treatment of chronic hepatitis C not only reduces morbidity and mortality due to decompensated liver cirrhosis and hepatocellular carcinoma (individual benefit), but also interrupts the transmission chain (community benefit). The peak of liver cirrhosis is expected for 2020[28] and cost-effectiveness of HCV treatment has been demonstrated[29,30]. Reinfection rate of former or current IDU is low[31,32]. The prescription of the new protease inhibitors telaprevir and boceprevir is restricted to gastroenterologists and infectious diseases specialists. In order not to withhold these new treatment options for HCV genotype 1 from patients in drug substitution programs, referral to a specialist must be facilitated. We are convinced that our project with its multidisciplinary and multiinstitutional study board will act as a facilitator.
The drop-out rate of the SCCS is high (31%), particularly among patients with IDU[16]. For these patients, coordinated efforts as provided by our initiative are of key importance. In contrast to the SCCS, we will also be able to determine HCV prevalence and incidence in drug substitution programs.

Facilities available: Both the clinics of Gastroenterology and Infectious Diseases in Baden and Aarau have an outpatient clinic experienced in HCV treatment. The mobile Fibroscan® the use of which will be shared by the institutions, will allow non-invasive measurement of liver fibrosis not only in the hospital, but also in the practice of the physician providing substitution treatment. HCV and HIV rapid test with fingerstick blood can lower the threshold for HCV/HIV screening, particularly in former intravenous drug users with limited venous access. Similarly, complete blood counts from capillary blood can lower the threshold to HCV treatment because the number of venous punctures for monitoring side effects can be reduced.

Collaborators

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