Final operational report for the research project ESTHER Switzerland 2016 G3

"Surveillance of Transmitted HIV-1 Drug Resistance in Drug-Naive and Newly Diagnosed Patients in Cameroon"

July, 31st, 2018

Project at a Glance:

Topic	Surveillance of Transmitted HIV-1 Drug Resistance in Drug-Naive and Newly Diagnosed Patients in Cameroon
Country	Cameroon
Goal	To build capacity in HIV genotypic resistance testing in Cameroon to successfully treat HIV positive individuals in the long run, and thus, restoring and maintaining their sexual and reproductive health.
Swiss institution	University Hospital Zurich Rämistrasse 100 CH-8091 Zurich Prof. Karin J. Metzner, M.D. Principal investigator University Hospital Zurich Division of Infectious Diseases and Hospital Epidemiology Rämistrasse 100 CH-8091 Zurich phone: +41 (0)44-255-3029 Email: Karin.Metzner@usz.ch
Partner Institutions	1. Bamenda Regional Hospital, Cameroon P.O. Box 863 Mankon, Mezam Division, Bamenda Dr. Mbuh Eyongetah Coordinator of HIV Treatment Centre Tel: +237675280190 e-mail: eyongetah2002@yahoo.com 2. Ndop District Hospital, Cameroon P.O. Box 04, Ndop Ngoketunjia Division Ms. Sama Bella Andong Nurse, HIV Treatment Centre Tel: +237675089829 3. Kumba District Hospital, Cameroon P.O. Box 31, Kumba Mrs. Besong Mpeh Lydia Nurse, HIV Treatment Center Tel: +237677874808 4. Ngaoundere Regional Hospital, Cameroon B.P. 455, Ngaoundere, Cameroon Mr. Orock Emmanuel, Laboratory Scientist, HIV Treatment Center Tel: +237676988569 5. Herbert Afegenwi Mbunkah (PhD student, from Cameroon) University Hospital Zurich Division of Infectious Diseases and Hospital Epidemiology Rämistrasse 100 CH-8091 Zurich phone: +41 (0)78-824-05-25 Email: HerbertAfegenwi.Mbunkah@usz.ch

The ESTHER Switzerland programme (https://www.esther-switzerland.ch)is implemented by the Institute of Social and Preventive Medicine (ISPM) of the University of Bern, on behalf of the Swiss Agency for Development and Cooperation SDC).

Background:

Surveillance data from 2015 showed a HIV prevalence of 4.5% in adults in Cameroon, i.e., more than 620'000 people are HIV-1 infected in Cameroon (UNAIDS. HIV Data and Statistics. http://aidsinfo.unaids.org/). Since 2016, every person diagnosed with an HIV infection is offered antiretroviral therapy (ART) free of charge. However, HIV drug resistance testing is still uncommon in Cameroon. Thus, in the near future, the benefits of ART can be jeopardized because of an increasing prevalence of drug resistant HIV.

Goal of our project:

"To build capacity in HIV genotypic resistance testing in Cameroon to successfully treat HIV positive individuals in the long run, and thus, restoring and maintaining their sexual and reproductive health."

From our findings, national and international policy makers will be informed by our results when/if they should consider: 1) changing antiretroviral regimens, 2) introducing individual pretreatment genotyping to guide therapy or 3) intensifying viral load monitoring to detect early failures associated with pre-ART HIV Drug Resistance.

Lead questions, we wanted to address

1. What is the recent prevalence of transmitted HIV-1 drug resistance (TDR) in the chosen study sites? Is the incidence of transmitted HIV drug resistance changing over time?
2. Which types of drug resistance mutations are most prevalent?
3. Can the HIV-1 genotypic drug resistance test be scaled up for routine diagnostic use in Cameroon?
4. What are the major transmission routes of HIV-1 and HIV-1 drug resistance mutations in the study sites?

Results/Outcome:

We could answer all lead questions in this study. We collected fingerprick dried blood spot samples (DBS) from newly diagnosed, ART naïve individuals at four hospitals in urban areas in Cameroon in the years 2015–2016. 83% of all samples could be successfully analysed. This success rate is in line with results of other studies using DBS (1, 2). The prevalence of transmitted HIV-1 drug resistance (TDR) was low (question 1) and we could not observe a time trend (question 1). The most common drug resistance mutations were associated with resistance to the first-line antiretroviral drugs of the groups of reverse transcriptase inhibitors (question 2). Heterosexual transmission of HIV-1 (>98%) is the major transmission route in Cameroon for both drug sensitive and drug resistant HIV-1 (question 4). These results are published in the Journal of Antimicrobial Chemotherapy as H.A. Mbunkah et al. (3).

Due to these very positive results, i.e., low prevalence of HIV-1 drug resistance, there is no requirement to 1) change the current antiretroviral regimens, 2) introduce individual pretreatment genotyping to guide therapy, or 3) intensify viral load monitoring to detect early failures associated with pre-ART HIV Drug Resistance.

Furthermore, Herbert Mbunkah, PhD student from Cameroon who developed, validated, and applied our dried blood spot (DBS)-based next-generation sequencing (NGS) HIV-1 drug resistance testing, also scaled the assay up, thus, it is now suitable to amplify and sequence up to 96 DBS in one sequencing run (question 3).

Thus, we could successfully address and answer all lead questions although the project took longer than anticipated as explained below in challenges.

By the end of this project we had the following intended project results (as stated in the proposal):

- Herbert Afegenwi Mbunkah from Cameroon would have acquired a PhD and enormous training on HIV-1 genotypic drug resistance testing

    Herbert Afegenwi Mbunkah has obtained enormous training on HIV-1 genotypic drug resistance testing. He will submit his PhD thesis by August 2018 and he will have his PhD defense approximately 6 weeks later in September/October 2018. This was delayed due to the challenges which are described below.

- An HIV-1 genotypic drug resistance test suitable for all HIV-1 subtypes and applicable to dried blood spots has been developed

    This has been achieved, please see above.

- The most recent data on transmitted HIV-1 drug resistance in the study sites would be established

    This has been achieved, please see above.

- At least 250 of the 368 enrolled HIV patients whose samples we could successfully amplify and sequence, will have results for the HIV-1 genotypic drug resistance test.

    This has been achieved, please see above.

- The HIV-1 genotypic drug resistance test developed will be scaled up to be more affordable for possible application in Cameroon for routine transmitted and also acquired HIV-1 drug resistance testing.

    This has been achieved, please see above.

Impact:

We successfully disseminated our finding through a comprehensive report, which we were able to publish in a renowed, peer-reviewed journal, the Journal of Antimicrobial Chemotherapy as H.A. Mbunkah et al. (3). All our four partner institutions are co-authors on this publication. The publication is attached to this report.

We are still in contact with all four hospitals and started a new project by expanding our analysis to the viral gene *integrase*, since it is planned to introduce integrase inhibitor soon in Cameroon as part of the antiretroviral regimens. Thus, it is of importance to perform a surveillance study.

Due to the unstable political situation, unfortunately, we cannot foresee how the future partnership will develop. Please see for more details the chapter "challenges". We were unable to train another healthcare staff from Cameroon in Zurich, mainly due to the unstable condition and the associated lack of funding. The situation did not impact most of our results/outcome (please see above) since this project was started before the unstable political situation started, however, at the moment, it is difficult to foresee what the future will look like.

Through the activities of our project, the training of Herbert Afegenwi Mbunkah and the published results of our study, we consider that we were able to successfully contribute to the building of capacities in HIV-1 genotypic resistance testing in Cameroon to successfully treat HIV-1 positive individuals in the long run.

Challenges:

We successfully built the capacity of HIV-1 genotypic resistance testing in Cameroon as declared in our aim of this study. However, part of our results were not obtained as planned and outlined in our proposal. Due to the politically very unstable situation in Cameroon, we were not able to travel to Cameroon and visit the study sites. The four hospitals are located in the Anglophone region of the country for which the Swiss Federal Department of Foreign Affairs (FDFA) and other countries declared travel warnings approximately 1 year ago, i.e., a few months after we got this project funded. When we submitted the proposal by September 2016, the situation was stable and it was not foreseeable that this will change so quickly. Until the beginning of this year, we were still hoping to be able to travel to Cameroon, but unfortunately, the political situation is unlikely to change for the better within the immediate future. Presently, there is a strong risk of a civil war developing in this part of the country.
Because of the political situation, we could not and cannot travel to Cameroon. Instead, we intensified other ways of communications, such as phone calls, Email, skype, etc., which was/is complicated due to the often-occurring interruptions in phone and internet accessibilities in the Anglophone part of Cameroon. This delayed the progress of our study by at least one year, however, thanks to Herbert Mbunkah's dedication and a significant increase of his workload, we were able to successfully finish all the main parts of our study.

Statement by Herbert A. Mbunkah

It has been a wonderful experience for me to be part of this partnership between our four collaborating hospitals in Cameroon and the Division of Infectious Diseases and Hospital Epidemiology at the University Hospital Zurich. It has been a pleasure on my side, being a key player in this project to get trained on HIV-1 drug resistance genotyping and to generate recent data for Cameroon on this subject. All members of the project team are highly motivated and very productive, reason why we successfully met our goals.

However, this project has not been a completely smooth ride all through. We encountered some obstacles which were unforeseeable. A major one being a severe political uprising in Cameroon, stemming from the English-speaking part of the country (where 3 of our 4 partner hospitals are located) who demand a change in the form of the state. This started in October 2016 and was met with a serious military crack-down on the civilian population. This has since deteriorated into an armed conflict on both sides today. We were fortunate to have received all our dried blood spot samples just before the conflict began. In 2017, the government of Cameroon intermittently cut internet and phone lines to the English-speaking parts of the country for months and this greatly affected our communication between Zurich and Cameroon. I could not reach the project staff in Cameroon to liaise with them for updates and clarifications on certain samples or questionnaires. This also extended to affect the delivery of patients' results from Zurich to Cameroon. This really slowed down the progress of the project and the timing of our publication and subsequently the thesis. We also had to postpone and later cancel our planned trip to Cameroon where we hoped to discuss about our current findings and possible future projects like the integrase resistance study which we are currently executing. The other obstacles faced were technical in nature and had to do with the difficulty in establishing the assay and the failure of 17% of samples to be amplified. These were however anticipated.

In all, we are very happy with the achievements we recorded and I am personally grateful to ESTHER Switzerland for the funding they provided to this partnership.

References:

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