Institution: Liverpool School of Tropical Medicine (LSTM)

Unit of Assessment: UOA2

Title of case study: Global Scale-Up of HIV Self-Testing: Reaching Vulnerable Populations Worldwide

Period when the underpinning research was undertaken: 2015 – 2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Frances Cowan	Professor, PI, Dep. Director STAR research, Zimbabwe research lead.	2016 –
Russell Dacombe	Senior Research Associate, Laboratory and Regulatory Capacity	2010 –
Nicola Desmond	Co-I Research lead social harms	2009 –
Peter MacPherson	PI Malawi HIV ST trial	2009 –
Webster Mavhu	Co-PI, STAR/BMGF research	2019 –
Euphemia Sibanda	Co-PI, Zimbabwe research lead	2019 –
Miriam Taegtmeyer	Professor, PI - Deputy director STAR research	2001 –
Victoria Watson	Research Associate, Diagnostics	2016 –

Period when the claimed impact occurred: 2015 – 2020

Is this case study continued from a case study submitted in 2014? Y/**N** NO

1. Summary of the impact (indicative maximum 100 words)

The Liverpool School of Tropical Medicine (LSTM) is at the forefront of HIV testing innovation, leading research to shape World Health Organization (WHO) guidelines. We are key partners in the Self-Testing in Africa (STAR) Initiative which aims to stimulate the market for HIV self-test kits through scale-up of HIV self-testing in Southern Africa. LSTM developed and rigorously evaluated delivery models in Malawi and Zimbabwe that catalysed a supportive regulatory, policy and funding environment. 88 countries now have HIV self-testing policies, and rapid scale-up has increased testing coverage among vulnerable, underserved and key populations worldwide. STAR has provided 4,500,000 HIV self-tests across Southern Africa and catalysed procurement of another 8,000,000 from major funders. Four manufacturers now have WHO pre-qualified HIV self-test kits on the world market.

2. Underpinning research (indicative maximum 500 words)

In 2019, 38,000,000 people were living with HIV with only 62% receiving treatment - due in part to suboptimal testing coverage. While awareness of HIV status has increased, it is still below 80% globally. Inequity in access and uptake remains, with men, young people, rural, key and vulnerable populations least likely to have tested. As coverage of testing increases, accessing those not previously tested gets more difficult and requires novel approaches. HIV self-testing (HIVST), where an individual performs their own test and interprets the result, can both reduce the testing gap and inequities in coverage. HIVST kits are diagnostic tests modified for individual use and distributed with instructional support. In 2014, there were no approved quality-assured HIVST kits nor regulatory infrastructure for such medical devices for use outside of the USA. There was little evidence from low resource settings on the accuracy, acceptability, feasibility and safety of introducing HIVST through various delivery models. The regulatory and policymaker discourse around HIVST focused on the potential for social harm. Evidence was required at country, regional and global level to stimulate the HIVST market, catalyse scale-up and inform global guidance.

LSTM (Taegtmeyer, MacPherson, Cowan, Desmond, Sibanda, Dacombe, Mavhu, Watson) with partners at London School of Hygiene and Tropical Medicine (LSHTM), University College London (UCL) and WHO has generated key evidence for the rapid global scale up of HIVST

through formative, early scale-up and implementation research to optimise delivery at scale, largely through the UNITAID-funded HIV STAR Initiative (between 2015 and 2021). Taegtmeyer and Cowan were both deputy research directors on STAR with LSTM leading the consortium-wide qualitative research network, policy and regulatory work and research on social harms. All research in Zimbabwe was undertaken by LSTM, and the Malawi research was jointly conducted by LSTM and LSHTM.

Critical formative research included studies on accuracy, acceptability, safety, costing and user preferences in various hard-to-reach populations including poor urban and rural populations and female sex workers (PI Cowan 2015-2020) plus legal, policy and regulatory review (PI Taegtmeyer, CoI Dacombe) [1]. STAR built on trials conducted by LSTM in Malawi between 2011 and 2013 (PI MacPherson, n=16,660), which showed high and sustained uptake of self-testing and greatly increased linkage to HIV treatment following home-based self-testing and treatment initiation in urban Blantyre [2,3]. Follow up 'STAR' trials of community-based HIVST distribution models (three cluster randomised trials) in Zimbabwe [4] (co PI Sibanda/ PI Cowan/ CoI Taegtmeyer/ Co PI Mavhu 2016-2020) and three trials in Malawi (PI MacPherson/ CoI Desmond 2016-2019) confirmed that making HIVST available within communities can rapidly increase testing coverage. In the Zimbabwean trial of community based delivery (PI Cowan 2016-2017), over 80,000 kits were delivered in 38 communities by incentivised community workers, increasing the percent of people 'ever tested' from 74% to 89% in a representative survey (n=7134), including among men and young people; the rate of antiretroviral therapy initiation increased by 27% [95% CI 17-39%] in linked facilities. Importantly, detailed mixed methods research to explore HIVST-related social harms was embedded in all these trials and confirmed the safety of HIVST (negligible testing-related violence or relationship dissolution and no suicides) (Taegtmeyer, Desmond) [5]. Acceptability and feasibility of providing HIVST for sex workers in Zimbabwe (Cowan 2016-2020) and Malawi (Desmond 2016-2019) found that sex workers could accurately test themselves and preferred self-testing when given the option, supporting scale up of HIVST to sex workers and other key populations in Zimbabwe and the region more widely [6]. LSTM through STAR was funded by the Bill and Melinda Gates Foundation (BMGF) to explore how pricing of HIVST kits affects user uptake among potential testers in poor urban and rural communities in a Zimbabwean trial (n=4,000) (PIs Sibanda, Cowan 2018) [7]. Uptake of testing was minimal in both rural and urban populations when the price of a voucher to retrieve an HIVST kit rose above USD0.5. Trials led by LSTM researchers have contributed to evidence showing that HIVST is likely to be cost-effective if introduced at scale (CoI Cowan and CoI Sibanda 2016-2020) [4].

LSTM (PI Taegtmeyer, CoI Dacombe) conducted qualitative research with regulatory and policy stakeholders in STAR countries [1]. The findings led to a tailored programme of capacity strengthening that brought regulators across the Southern African region together with national reference laboratories, HIV policymakers and WHO in the development of convergent regulatory frameworks for in vitro diagnostics. Legal mandates and national regulation led to inclusion of HIVST within national HIV testing policies (Malawi 2018, Zambia 2018, Zimbabwe 2018). In addition, they undertook research to compare methods for adapting instructions for use to individual contexts and to assess feasibility of post market surveillance through re-reading of used kits. Research and implementation findings fed directly into the WHO pre-qualification process and also combined to inform a user-friendly toolkit targeted at programmes for optimising the introduction of HIVST into a national HIV testing strategy. The resultant regulatory progress strengthened the health system response beyond HIV to set the stage for the introduction of other self-testing and point-of-care diagnostics including for COVID-19.

3. References to the research (indicative maximum of six references)

1. **Dacombe RJ**, **Watson V**, Nyirenda L, Madanhire C, Simwinga M, Chepuka L, Johnson CC, Corbett EL, Hatzold K, **Taegtmeyer M**. Regulation of HIV self-testing in Malawi, Zambia and Zimbabwe: a qualitative study with key stakeholders. J Int AIDS Soc. 2019. DOI: 10.1002/jia2.25229

2. **MacPherson P**, Lalloo DG, Webb EL, Maheswaran H, Choko AT, Makombe SD, Butterworth AE, van Oosterhout JJ, **Desmond N**, Thindwa D, Squire SB, Hayes RJ, Corbett EL. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: a randomized clinical trial. JAMA. 2014. DOI: 10.1001/jama.2014.6493
3. Choko AT, **MacPherson P**, Webb EL, Willey BA, Feasy H, Sambakunsi R, Mdolo A, Makombe SD, **Desmond N**, Hayes R, Maheswaran H, Corbett EL. Uptake, Accuracy, Safety, and Linkage into Care over Two Years of Promoting Annual Self-Testing for HIV in Blantyre, Malawi: A Community-Based Prospective Study. PLoS Med. 2015. DOI: 10.1371/journal.pmed.1001873
4. Mangenah C, Mwenge L, Sande L, Ahmed N, d'Elbée M, Chiwawa P, Chigwenah T, Kanema S, Mutseta MN, Nalubamba M, Chilongosi R, Indravudh P, **Sibanda EL**, Neuman M, Ncube G, Ong JJ, Mugurungi O, Hatzold K, Johnson CC, Ayles H, Corbett EL, **Cowan FM**, Maheswaran H, Terris-Prestholt F. Economic cost analysis of door-to-door community-based distribution of HIV self-test kits in Malawi, Zambia and Zimbabwe. J Int AIDS Soc. 2019. DOI: 10.1002/jia2.25255
5. Kumwenda MK, Johnson CC, Choko AT, Lora W, Sibande W, Sakala D, Indravudh P, Chilongosi R, Baggaley RC, Nyirenda R, **Taegtmeyer M**, Hatzold K, **Desmond N**, Corbett EL. Exploring social harms during distribution of HIV self-testing kits using mixed-methods approaches in Malawi. J Int AIDS Soc. 2019. DOI: 10.1002/jia2.25251
6. Napierala S, **Desmond NA**, Kumwenda MK, Tumushime M, **Sibanda EL**, Indravudh P, Hatzold K, Johnson CC, Baggaley RC, Corbett L, **Cowan FM**. HIV self-testing services for female sex workers, Malawi and Zimbabwe. Bull World Health Organ. 2019. DOI: 10.2471/BLT.18.223560
7. Chang W, Matambanadzo P, Takaruza A, Hatzold K, **Cowan FM**, **Sibanda E**, Thirumurthy H. Effect of Prices, Distribution Strategies, and Marketing on Demand for HIV Self-testing in Zimbabwe: A Randomized Clinical Trial. JAMA Netw Open. 2019. DOI: 10.1001/jamanetworkopen.2019.9818

4. Details of the impact (indicative maximum 750 words)

LSTM's HIVST research has directly contributed to increased coverage of HIV testing in Southern Africa and worldwide, particularly among vulnerable rural, urban and key populations by supporting development of global, regional and national normative guidance for HIVST (between 2015 and 2017), catalysing the market for HIVST kit manufacture (4 HIVST kits are now pre-qualified by WHO) and galvanising global scale up of implementation supported by major funders (BMGF, US President's Emergency Plan for AIDS Relief (PEPFAR) and Global Fund for AIDS TB and Malaria (GFATM)) [1]. By 2020, 88 countries globally had HIVST policies in place (including all six STAR countries plus an additional 17 in Africa); all of which have been directly or indirectly involved in STAR through attending regional dissemination workshops. The global HIVST market was approximately 20,000,000 at the end of 2020.

Increasing the proportion of people living with HIV being aware of their HIV status

More than 2,000,000 HIVST kits were procured and distributed through STAR in Malawi, Zambia and Zimbabwe between 2016 and end of 2020 (accounting for 37%, 22% and 38% of all testing undertaken in these countries between 2018 and 2020). STAR was the only source of HIVST kits until 2018, catalysing additional investment through GFATM and PEPFAR after that. STAR research has shown HIVST to be acceptable, safe, effective and accurate. Community distribution of HIVST has facilitated testing of many first-time testers and provided a step change in the rate of ever testing and was associated with an increase in uptake of testing among individuals known to have poor uptake of testing: men, young people and those of religions opposed to allopathic medicine. Over the course of STAR both Zimbabwe and Malawi made demonstrable gains in terms of UNAIDS target (90% of HIV positive people should be aware of their HIV status), with knowledge of HIV positive status rising from 74% and 72% in 2016 in Zimbabwe and Malawi, to over 90% in both countries by 2019 [2].

Influencing Global and National policies and guidelines on HIVST

In 2016, using evidence from STAR, WHO recommended use of HIVST for the first time [3]. LSTM played a leading role in supporting four African countries to adapt these guidelines for regional and national use through a series of workshops run with WHO between 2016 and 2019, which catalysed inter- and intra-country collaboration between regulators, policy makers and national reference laboratory representatives in Malawi, Zimbabwe, Zambia and South Africa. Key stakeholders developed timebound action plans, identifying the necessary steps required for HIVST at national scale. National guidelines and regulation on HIVST were developed and launched in Zimbabwe in 2016, Malawi in 2018, Zambia in 2018 and South Africa in 2017 [4]. This work facilitated development and implementation of national regulatory and policy frameworks for HIVST (and for use of in-vitro medical devices more generally) and provided a framework for other countries to use going forward. A regional workshop held by STAR and WHO in Nairobi Kenya in 2017 was attended by over 160 key stakeholders from 25 different African countries. Workshop participants forged networks and engaged in south-south knowledge exchange, which allowed countries to work collaboratively to transform normative HIVST guidance into implementation strategies and led to several within-country learning visits between non-STAR and STAR countries to guide implementation. 23 African countries now have HIVST guidelines in place and several more are in the process of development, with many sharing and building on tools developed as part of STAR [5].

Global donors such as GFATM, UKAID and PEPFAR now fund and promote HIVST within their HIV programmes. In response to the COVID19 pandemic, these funders have further expanded HIVST to support testing while maintaining physical distancing. LSTM are acknowledged for their contributions to HIVST.org (the principal HIVST digital resource set up by WHO – Peter MacPherson is listed as a contributor). Training materials and toolkits developed by LSTM are available publicly on STAR and HIVST.org websites and are in use in Africa and Asia.

Increasing commercial involvement and reducing test kit prices

When LSTM and WHO co-hosted the first international meeting on HIVST in Geneva in 2013, there were no prequalified products for procurement in low-income countries, and few manufacturers were interested in entering the market. Structural barriers to market entrance for HIVST devices were reduced by the development of WHO Pre-qualification and programmatic guidance. This was underpinned by LSTM's contribution to the WHO Technical Specifications Series for submission to WHO Prequalification in 2016 and the WHO Guidelines on HIVST and Partner Notification Supplement to Consolidated Guidelines on HIV Testing Services in 2018 [2, 6]. Market barriers for HIVST manufacturers were eased by working with STAR countries to ensure that HIVST guidelines and device registration regulations were convergent [7].

The OraQuick® HIV Self-Test was the first to be pre-qualified by WHO in 2017 having been available in the US since 2012. Evidence on costs and pricing generated by LSTM in Zimbabwe and Malawi contributed to BMGF's decision to fund a buy-down of the OraQuick® HIV Self-Test kit reducing the price from USD3.15 to USD2 per kit in 50 low income countries to promote self-testing scale up and market development [8].

From the beginning of 2020, there are now four prequalified HIVST kits available listed for procurement for low income countries through GFATM (one oral fluid test OraQuick® HIV Self-Test, OraSure Technologies Inc USA/Thailand and three blood based (INSTI® HIV Self-Test, BioLytical Laboratories, Canada; SURE CHECK HIV Self-Test, Chembio Diagnostic Systems, USA; Mylan HIV Self-Test [former Atomo HIV Self-Test], Atomo Diagnostics Pty Ltd, Australia)). LSTM through research in Zimbabwe was involved in the adaptation of all four manufacturers' instructions for use for Southern African settings; we identified common errors and developed demonstration materials (now incorporated into manufacturers product inserts) and worked with manufacturers to ensure that intended users are able to correctly perform and interpret tests in the privacy of their own homes, allowing scale up to the remotest of areas and hardest to reach populations [9]. LSTM's research into the visual stability of late read oral fluid test results [10] informed WHO guidance on post market surveillance strategies for HIVST [10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Realizing the potential of HIV self-testing for Africa: lessons learned from the STAR. Guest Editors: Vincent J Wong, Nathan Ford, Kawango Agot. https://www.iasociety.org/Portals/0/Files/JIAS_Vol22-S1_complete_file.pdf

Increasing the proportion of people living with HIV being aware of their HIV status

2. 2020 UNAIDS Global AIDS update https://www.unaids.org/en/resources/documents/2020/global-aids-report

Influencing Global and National policies and guidelines on HIVST

3. WHO HIVST guidelines 2016, Guidelines on HIV Self-Testing and Partner Notification. Supplement to Consolidated Guidelines on HIV Testing Services. Geneva: World Health Organization; 2016. https://www.who.int/hiv/pub/self-testing/hiv-self-testing-guidelines/en/

4. Guidelines on HIV Self Testing: Malawi: Ministry of Health and Population, Malawi HIV Self Testing Operational Guidelines. 2018, Zambia: The Ministry of Health and Population: Lilongwe; South Africa: South African HIV self-testing policy and guidance considerations DOI: 10.4102/sajhivmed.v18i1.775; Zambia: Consolidated Guidelines for Prevention and Treatment of HIV Infection 2018 ; Zimbabwe: Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe, 2016. https://depts.washington.edu/edgh/zw/vl/project-resources/ZIM_ART_Guidelines_2016_-_review_final.pdf

5. HIVST.org (http://hivst.org/) website contains information on national HIV self-testing policies

Increasing commercial involvement and reducing test kit prices

6. HIVST WHO Technical Specifications Series for submission to WHO Prequalification – Diagnostic Assessment: Human Immunodeficiency Virus (HIV) rapid diagnostic tests for professional use and/or self-testing. Geneva: World Health Organization; 2016. https://www.who.int/diagnostics_laboratory/guidance/technical_specification_series/en/

7. Market and technology landscape for HIV rapid diagnostic tests for self-testing . 3rd Edition 2018. https://unitaid.org/assets/HIV-Rapid-Diagnostic-Tests-for-Self-Testing_Landscape-Report_3rd-edition_July-2017.pdf

8. HIV self-testing strategic framework: a guide for planning, introducing and scaling up. WHO. https://apps.who.int/iris/bitstream/handle/10665/275521/9789241514859-eng.pdf?ua=1

9. Simwinga M, Kumwenda MK, Dacombe RJ, Kayira L, Muzumara A, Johnson CC, Indravudh P, Sibanda EL, Nyirenda L, Hatzold K, Corbett EL, Ayles H, Taegtmeyer M. Ability to understand and correctly follow HIV self-test kit instructions for use: applying the cognitive interview technique in Malawi and Zambia. J Int AIDS Soc. 2019. DOI: 10.1002/jia2.25253

10. Watson V, Dacombe RJ, Williams C, Edwards T, Adams ER, Johnson CC, Mutseta MN, Corbett EL, Cowan FM, Ayles H, Hatzold K, MacPherson P, Taegtmeyer M. Re-reading of OraQuick HIV-1/2 rapid antibody test results: quality assurance implications for HIV self-testing programmes. J Int AIDS Soc. 2019. DOI: 10.1002/jia2.25234