BMJ Open Acquired HIV drug resistance among children and adults receiving antiretroviral therapy in Tanzania: a national representative survey protocol

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ABSTRACT

Introduction Tanzania is making an enormous effort in scaling-up of antiretroviral therapy (ART). However, people living with HIV (PLHIV) continue to succumb to the challenge of drug resistance. Evidence on drug resistance for a national survey is unavailable in Tanzania. Therefore, we sought to assess viral suppression (vs) rates and magnitude of acquired drug resistance (ADR) among PLHIV.

Methods and analysis A national survey will be conducted from 26 July to 29 October 2021 in 22 regions, recruiting 2160 participants. These will include adults on ART for 9–15 months and ≥48 months and children on ART for 9–15 months and ≥36 months. A standardised questionnaire will capture participants' demographic and clinical data. Plasma and dried blood spot will be prepared for viral load testing and drug resistance genotyping.

Statistical analyses to determine the burden of ADR, characteristics and factors associated therewith will be done using STATA V.15.

Ethics and dissemination Ethical approval has been obtained from the National Health Research Ethics Committee of Tanzania (NIMR/HQ/R.8a/Vol.IX/3432). Appropriate participant informed consent or parental consent and assent will be obtained. Dissemination will include a survey report, conference presentations, policy briefs and peer-reviewed publications.

INTRODUCTION

Tanzania's HIV burden stands at a prevalence of 4.7% among adults aged 15–49 years, as reported in 2018, translating to about 1.6 million people living with HIV (PLHIV).¹ In the last three decades, the country has made significant strides, adopting global fast track targets to ensure that 90% of people know their HIV status, 90% are on treatment and 90% achieve virological suppression. The Tanzania Health Impact National Survey reported 90/90/90 progress among PLHIV aged 15 years and older, which were 60.6%,

Strengths and limitations of this study

- A two-stage cluster sampling will generate nationally representative estimates of VS and ADR.
- Use of dried blood spots (DBS) is feasible and cost-effective in terms of logistics for collection, storage and transportation of a large-scale survey in our setting.
- Increasing VS due to the Dolutegravir rollout may decrease the number of eligible participants for genotyping.
- Viral RNA in DBS is susceptible to degradation due to high humidity in our settings; plasma samples will supplement DBS with amplification challenges.

93.6% and 87%, respectively.² These were population-based estimates, and recently in 2019, UNAIDS reported Tanzania estimates of 1.6 million PLHIV aged 15 years and 93 000 children aged 0–14 years. Of these, 83% knew their HIV status, 75% were on antiretroviral therapy (ART) and 69% had viral suppression.³ This demonstrates good progress with the first target but lagging behind with the second and third targets. The reason may be due to existing gaps in linkage to care after HIV testing, low retention rates after ART initiation^{4,5} and the emerging drug resistance challenge.

Viral non-suppression reflects treatment failure, associated with a number of factors including, non-adherence to therapy, treatment interruption, delays in switching to efficacious drugs, drug resistance or a combination of some or all, requiring differentiated clinical management.^{6–8} Particularly, in resource limited settings, it has been reported that virologic failure (VF) occurred between 19.3% and 32%.⁸ In Tanzania, studies

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have reported VF ranging from 7.0% to 14.9% among PLHIV.^{8–10} Moreover, a recent study from 15 sites in Tanzania found that 38.8% of children had VF and ADR was prevalent in 84.4%.⁹ Data from the nationally representative survey with ADR mutation trends may, therefore, be more robust in informing policy and planning of interventions curbing the seemingly increasing burden of VF. Routine HIV drug resistance testing to guide selection of ART either during initiation or while on ART is not available in Tanzania.^{10–11} The WHO recommends resistance testing for PLHIV with confirmed VF on Protease-inhibitor-based second-line ART coupled with enhanced adherence counselling followed by a confirmatory viral load (VL) test for resource-limited countries.^{12–13} HIV treatment has been changing over time owing to advances in care and treatment. In Tanzania, five classes of antiretroviral drugs are available. These are nucleoside reverse transcriptase inhibitors (NRTIs) Zidovudine (AZT), Lamivudine (3TC) and Abacavir (ABC); non-NRTIs (NNRTIs) Efavirenz (EFV); nucleotide reverse transcriptase inhibitors (NRTIs) Tenofovir (TDF); protease inhibitors (PIs) Atazanavir (ATV) and Lopinavir (LPV) and pharmacokinetic enhancer Ritonavir (r).¹⁴ In 2019, integrase strand transfer inhibitors (INSTIs), Dolutegravir (DTG) and Raltegravir (RAL) were introduced following high rates of pretreatment drug resistance with NNRTIs class.¹⁵

Tanzania, like other countries, requires a robust surveillance of emerging ADR due to challenges in meeting the fast track and elimination targets. Importantly, surveillance of ADR in HIV populations receiving first-line ART is critical to assessing HIV care and treatment programme quality and informing the selection of second-line regimens. Therefore, the National AIDS Control Program (NACP) planned for a national-wide representative survey to determine prevalence of ADR, drug resistance patterns and factors associated thereof. This protocol is designed to undertake this important endeavour, and the findings will reflect ART programme quality and inform national policy and ART management guidelines.

METHODS AND ANALYSIS

Survey design

This cross-sectional survey is designed to assess VS and Human Immunodeficiency Virus drug resistance (HIVDR) among individuals on ART. Adults on ART for 9–15 months and ≥48 months; and children on ART for 9–15 months and ≥36 months will be enrolled. We will employ the WHO recommendation for national surveys to estimate the prevalence of VS and ADR at the early time point of 9–15 months and the late time point of >36 months in children and 48 months in adults. The survey will be conducted for a period of 3 months, from 26 July to 29 October 2021, in 22 regions of the Tanzania mainland. The selected regions include Dodoma, Dar es Salaam, Morogoro, Pwani, Kagera, Mara, Mwanza, Geita, Arusha, Kilimanjaro, Tanga, Iringa, Katavi, Mbeya, Njombe, Rukwa, Songwe, Mtwara, Ruvuma, Kigoma, Shinyanga

and Tabora. These regions were selected as national representatives, having 90% of the patient population.

Survey population selection criteria

The survey will involve participants aged 15 years and above as adults and less than 15 years as children. The inclusion criteria will be based on the four groups of participants. The first group shall include adults who have been on ART for 12 ±(3) months with signed informed consent and are still on ART at the time of enrolment, regardless of site of therapy initiation. The second group shall be adults receiving ART for at least 48 months at the time of enrolment, regardless of site of ART initiation, who will provide informed consent. The third group shall be children (18 months and ≥ 15 years with a caregiver/parent to consent for child's participation) receiving ART for 12 (±3) months and are still on ART at the time of enrolment, regardless of site of ART initiation. The fourth and last group shall be children (18 months and <15 years with a caregiver/parent to consent for child's participation) receiving ART for at least 36 months and are still on ART at the time of enrolment, regardless of site of ART initiation. We will exclude participants who meet inclusion criteria but transferred in without records.

Survey site selection

Site selection was conducted by listing all facilities providing ART services to PLHIV in Tanzania, and then a cluster sample design was employed with random site selection within each cluster. The targeted number of sites was based on the desired precision of the prevalence estimate and allowed for site drop out. Participants to be enrolled in each site were fixed, as determined by the number of sites selected using probability proportional to size (PPS). To perform PPS using nationally representative data, the number of clients currently on ART from July to September 2017 was extracted from the District Health Information System, which represents all the facilities in Tanzania. In total, 2620 facilities reported providing HIV services. After ranking them by the number of clients currently on treatment, 982 facilities, representing 90% of the patient population, were included in the sampling frame. The 982 sites were listed according to the region and zone in which they were located, along with the number of clients <15 and ≥15 years who were current on ART, and a column was added to calculate the cumulative number current on ART (adding the previous sites each time). The total cumulative number of 768 907 was then divided by the number of facilities that were included in this survey (36)—768 907/36=21 359—in order to get the sampling interval. That number was placed into a random number generator and yielded 12 628, which was used to identify the first site. The sites selected for the survey are presented in online supplemental table 1.

Sample size estimation

Sample size calculations aimed to ensure that the precision of the prevalence estimate for versus among ART

clients, defined as the half-width of the 95% CI, is 5%, if all the assumptions are correct. Based on the plans to include 30 clinics with a buffer of 20% of facilities (to account for potential facility dropout), a total of 36 facilities will be included in this survey. The sample size for this cross-sectional survey will be 2160 ;1080 children and 1080 adults (online supplemental table 2).

Survey preparation

A site assessment was done to assess the availability of eligible adults and children on ART at four different time points as per inclusion criteria; site database, qualified research assistants (data and laboratory technicians) at the health facility, laboratory infrastructure and specimen transportation logistics. The expected outcome was to formulate a specimen flow map (sample collection–processing–storage–transportation) and designating survey facilities that will qualify as either hubs or spokes. The findings of the site assessment are summarised in online supplemental table 3.

Selection of data collectors was done to include two healthcare providers (data and laboratory technicians experienced with HIV Care and Treatment Clinic (CTC) services from each of the health facilities for the survey data collection activity.

Training of data collectors and survey supervisors for 5 days was done for data collectors and supervisors (at national and regional level) on the survey protocol, standard operating procedures (SOP) and data extraction. The trained survey assistants conducted a pretest for the questionnaire in both Swahili and English language versions using an open data kit (ODK) software.

Survey supervision will be done by two supervision sessions from a national survey team (survey coordinator, PI, national laboratory representatives and other NACP staff) and a regional survey team (respective regional laboratory technicians and regional AIDS coordinators). The supervision sessions will be conducted during the first week and week 8 of data collection. The aim of the survey supervision is to make sure that data collection process is done according to the survey SOPs and to identify and solve challenges that will be encountered during data collection.

Data collection and management

Survey data collectors will assess the facility database for eligible clients and then contact them to remind them regarding their scheduled visits. Data collection will begin on 26th July 2021 for three consecutive months until 29th October 2021. Eligible participants will be enrolled as they attend their scheduled CTC visits. Participants will be given health education and information regarding the survey by the ART nurse and the data technician will then invite the eligible clients to participate in the survey. Informed consent from adults over 18 years will be obtained. In addition to parental consent, written assent will be sought from all children under 18 years as determined by national standards in Tanzania, except for

emancipated minors. These are defined as adolescents aged 15–17 whose circumstances allow them to consent for themselves. One copy of written informed consent/assent forms will be given to the participant and one kept under a locked cabinet at each survey site and at the end of the survey, signed consent/assent forms will be collected altogether to be stored as source documents. Participants' demographic and clinical variables, such as the date of ART initiation, initial ART regimen, CD4 cell count at ART start, latest CD4 count at survey enrolment, patient ART history (first- and second-line ART regimens).

Thereafter, data technicians will administer survey questionnaires to the participants by using ODK software. The questionnaire will include the determinants of non VS and ADR such as adherence, food security, depression, quality of life, family support, socioeconomic status and distance travelled to the clinic. Each survey assistant will send the completed survey participant questionnaire to the central server with a password-protected database. On the electronic survey questionnaire, survey participants are identified by a unique identifier and no participant names will be stored in the survey database. Thereafter, the participant will be directed to the laboratory for sample collection as per survey protocol (online supplemental figure 1).

Sample collection and specimen processing

Each participant will be assigned a survey identification with 10 barcodes. One barcode will be placed on the participant's CTC paper-based file, one on the client's survey lab request form, two EDTA tubes, three barcodes on three plasma cryovials and two barcodes on two dried blood spot (DBS) cards. About 10 ml of whole blood will be collected from each participant and 5 ml of whole blood into each of two EDTA tubes. For a spoke facility, the samples will be transported immediately to a hub facility, where samples will be processed immediately for a facility designated as both a spoke and a hub. Two DBS cards and three plasma vials will be prepared, whereby one plasma vial will be used for VL testing. The DBS will be made at the survey sites following a standardised protocol¹⁶ by dropping 100 µl of whole blood into each of the five preprinted circles in the Whatman 903 card, drying overnight and then packaging with desiccants and a humidity indicator card. The package will be kept at an ambient temperature in a dry place with no direct exposure to sunlight. The DBS cards will then be transported weekly from the survey sites by courier and delivered to Muhimbili University of Health and Allied Sciences (MUHAS) in Dar es Salaam, where they will be stored at –80°C until shipment.

One DBS card will be treated as a backup for longer storage for HIV VL and drug resistance testing, and the second DBS card will be stored temporarily at MUHAS awaiting shipping for HIVDR testing at the designated WHO laboratory. One plasma vial will be kept as a backup in case DBS specimens are found not suitable

for genotyping, and one plasma vial will be stored at MUHAS for future studies. On a weekly basis, the corresponding study coordinator (one of the data collectors) at each survey site will send DBS packages (comprising DBS cards and their corresponding specimen inventory forms) to MUHAS by road transportation by the chosen courier (TUTUME worldwide Limited). This courier has been providing specimen transportation services for clinical research studies in Tanzania. In addition, the courier service providers have been trained and oriented on how to handle the DBS and plasma package during transportation. All collected samples will be stored as per WHO protocol third revision 2019.¹⁶ These samples will be transported weekly to the microbiology laboratory at MUHAS, where an initial quality control check of the samples will be performed, and then the samples will be stored until a significant number is achieved before performing VL testing. Although plasma is considered to be the most appropriate specimen for HIVDR genotyping, we have chosen DBS, which is the WHO-recommended specimen for surveillance purposes in resource-limited settings. DBS is easily transported at ambient temperature from survey sites to a long/short-term storage facility and later to the WHO-accredited laboratory for genotyping outside Tanzania. In the event that viral RNA amplification and sequencing fail, plasma samples will be used as a backup. Furthermore, we will store one DBS sample and one plasma sample for future studies.

Survey participants' samples with VL of 1000 copies/mL will be sent to a WHO-accredited laboratory as per protocol (online supplemental figure 1). HIVDR genotyping will target the complete polymerase gene; protease (PR)-reverse transcriptase (RT) and integrase (IN) regions. The extraction of HIV-1 RNA from DBS will be performed, following standard methods followed by quality control reagents for two amplification reactions that target parts of the HIV-1 PR-RT gene regions and the IN region. Briefly, a nested reverse transcriptase-PCR protocol will be used, starting from extracted RNA, to separately amplify the PR-RT and IN regions of the HIV pol gene. Sequencing will be done using a conventional sequence-based standardised genotyping procedure according to HIVResNet guidelines, by using the Sanger sequencing technique (3730 XL, Genetic Analyzer; Applied Biosystem). The generated sequences will be assembled and aligned by using Seqscape software V.2.7 and each sequence will be manually checked to ensure quality and then the data will be uploaded into the Stanford University HIV drug resistance database (HIVdb). HIVdb, a public database that stores and analyses HIV drug resistance data, will be used to determine antiretroviral (ARV) drug susceptibility classified as potential low-level resistance, low, intermediate or high levels of resistance to one or more of the ARV drug classes used in Tanzania. Univariate and multivariate logistic regression models will be used to analyse for associations between HIVDR mutations (clients having at least one ARV class drug resistance mutation) and factors including

adherence, psychosocial and socioeconomic. Factors with a p value of less than 0.1 will be subjected to multivariate logistic regression analysis.

Quality assurance

The ADR survey team will implement quality assurance procedures, making sure that we collect high-quality data and minimising errors by using predefined SOPs. These SOPs were introduced during training for data collection and laboratory specimens' procedures to ensure accurate and consistent measurements throughout the survey. The survey team supervisors and survey assistants are emphasised to adhere to explicit standards of data quality following each step in the SOPs. During data collection process, there will be two supervision and mentorship visits at each survey site for systematic monitoring. Each supervisor will assess whether all the SOPs are followed and document the findings. Debriefing will be done to review findings from all survey sites and discuss corrections and provide a way forward prior to the majority of the data being collected. Participants' data will be sent to the main server by the data technician at the survey site daily and downloaded by the data technician at MUHAS and then checked on a daily basis for completeness and consistency. Trained laboratory technicians will perform quality check for DBS and plasma samples collected during sample processing and before transportation, and on receipt at MUHAS microbiology laboratory, checking for plasma sample volume, labelling, transport condition for DBS as per WHO 2019 protocol.¹⁷

Data management and analysis

Data from the ODK will be imported into Excel and data merging will be done with those from the laboratory (VL and HIVDR) results. STATA V.15 software will be used to perform all the statistical analyses. The primary survey outcomes and categorical secondary outcomes will be analysed using a logistic regression model. For HIVDR, sequence data will be scrutinised manually and aligned, and the sequences will be entered into the HIV database's Genotype Resistance Interpretation Algorithm and analysed. The Stanford HIVdb¹⁷ will be used for the assignment of HIVDR and to predict drug susceptibility patterns to the resistance viral strains. The report will interpret the drugs or drug classes used in Tanzania and describe the five levels of resistance, which are susceptible, potential low-level resistance, low-level resistance, intermediate resistance and high-level resistance.

Patient and public involvement

No patient involvement was done during the development of the survey design. The results of versus and ADR will be sent back to all survey sites for clinical management accordingly. Selected survey participants will attend the dissemination meeting at the end of the survey.

Ethics and dissemination

Ethical approval for this survey has been obtained from the National Institute for Medical Research (NIMR) of

Tanzania (NIMR/HQ/R.8a/Vol.IX/3432). In addition, permission has also been obtained from the Permanent secretary of Tanzania local government. Participants' details and their respective results will be coded using survey ID codes that are linked with the clients' CTC identification. The available electronic data files and computers will be password protected. No identifying information will be included in the data that any of the coinvestigators receive. All study-related materials, including data capture forms, logs and informed consent, will be stored in a secure locked cabinet at the NACP office in Dodoma, Tanzania. Study materials will be kept for 3 years after the survey has been completed, after which point, they will be destroyed.

Findings from this survey will be shared through a survey report, presentation to scientific conferences and clinical subcommittee of NACP, peer-reviewed publications and policy briefs targeting ART national policymakers. The authors will provide recommendations, including time intervals for subsequent national drug resistance surveys.

DISCUSSION

Access to combination ART in Tanzania and elsewhere has improved greatly over recent years and is highly associated with good clinical outcomes.^{18–20} However, suboptimal VS and the presence of HIVDR in populations receiving ART significantly affect treatment outcomes, resulting in treatment failure.^{21–22} HIVDR has been previously reported among adults and children experiencing treatment failure in Tanzania,^{9–10–23} this reflects gaps in ART programme quality, including inadequate VL monitoring,²⁴ interruptions in drug supply and low retention, similar to other African countries.²⁵ Timely identification and monitoring of ART failure from any cause should be obligatory to escalate ART benefits and to prevent further complications. Tanzania adopted the WHO recommendation for a transition from NNRTI-based first line to DTG-based, which was implemented in 2019. Thus, we anticipate a higher rate of VS due to the effectiveness of DTG and the high genetic barrier to resistance.²⁶ The high rate of VS due to DTG rollout may decrease the number of eligible participants for genotyping in our survey. Importantly, HIV programmatic monitoring for drug resistance is paramount to assess the magnitude and predict the transmission of HIVDR.

Notably, this surveillance will use DBS samples for genotyping because DBS can be widely used for population-based surveillance in resource-limited countries. Despite the fact that DBS samples are considered field-friendly and require fewer resources, methodological genotyping limitations may arise. The reduced sensitivity of viral RNA amplification is caused by nucleic acid degradation, small input volumes and impaired nucleic acid extraction.¹⁶ The survey team has planned to mitigate this by ensuring quality assurance for optimal DBS collection, storage and shipping conditions, thus meeting the WHO-recommended standard for HIVDR surveys. In addition,

we will collect plasma samples that will serve to supplement DBS samples found unsuitable for genotyping. Another limitation includes the low VL below the limit of amplification sensitivity of most DBS-based genotyping assays. The DNA amplification success is more common for samples with high plasma VL. DBS may also contain some proviral DNA from the PBMCs. The DNA when present is more stable than RNA in DBS, because viral RNA in the plasma component may be degraded faster than proviral DNA under suboptimal DBS storage and humid conditions. Therefore, when DBS is stored under optimal conditions, it may result in amplification of the proviral DNA when present. However, there is a high concordance between sequences obtained from plasma viral RNA versus proviral DNA.

Without surveillance, PLHIV who are exposed to a failing drug regimen for an extended period develop accumulation of drug resistance mutations (DRMs),²⁷ exposing them to morbidity and mortality.¹¹ Additionally, HIVDR surveillance will inform and guide standards of PLHIV treatment and improve healthcare policies, particularly in resource-limited settings where routine drug resistance testing is not available. Therefore, surveillance of ADR provides evidence that can be used to optimise patient and population-level treatment outcomes as recommended by the WHO; the nationally representative surveys among different populations, including adults and children.²⁸ Findings from this survey will inform ART programme implementation with specific evidence-based recommendations thereof.

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REFERENCES

- Exavery A, Charles J, Barankena A, *et al*. Art use and associated factors among HIV positive caregivers of orphans and vulnerable children in Tanzania. *BMC Public Health* 2020;20:1251.
- Tanzania HIV Impact Survey. A population based HIV impact assessment 2016-2017. Available: https://www.nbs.go.tz/nbs/takwimu/this2016-17/Tanzania_SummarySheet_English.pdf [Accessed 15 May 2020].
- UNAIDS. Global HIV & AIDS statistics — 2019 fact sheet, 2019/2020. Available: <https://www.unaids.org/en/resources/fact-sheet> [Accessed 13 Jun 2020].
- AVERT. HIV and AIDS in Tanzania [report], 2020. Available: <https://www.avert.org/printpdf/node/40615/05/2021> [Accessed 15 May 2021].
- B. Nachege J, C. Marconi V, U. van Zyl G, *et al*. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. *Infect Disord Drug Targets* 2011;11:167–74.
- Nega J, Taye S, Million Y, *et al*. Antiretroviral treatment failure and associated factors among HIV patients on first-line antiretroviral treatment in Sekota, northeast Ethiopia. *AIDS Res Ther* 2020;17:39.
- Getawa S, Fentahun A, Adane T, *et al*. Antiretroviral treatment failure and associated factors among HIV-infected children on antiretroviral therapy: a retrospective study. *HIV Aids* 2021;13:229–37.
- Vanobberghen FM, Kilama B, Wringe A, *et al*. Immunological failure of first-line and switch to second-line antiretroviral therapy among HIV-infected persons in Tanzania: analysis of routinely collected national data. *Trop Med Int Health* 2015;20:880–92.
- Muri L, Gamell A, Ntamatungiro AJ, *et al*. Development of HIV drug resistance and therapeutic failure in children and adolescents in rural Tanzania: an emerging public health concern. *AIDS* 2017;31:61–70.
- Mziray SR, Kumburu HH, Assey HB, *et al*. Patterns of acquired HIV-1 drug resistance mutations and predictors of virological failure in Moshi, Northern Tanzania. *PLoS One* 2020;15:e0232649.
- Takou D, Fokam J, Teto G, *et al*. HIV-1 drug resistance testing is essential for heavily-treated patients switching from first- to second-line regimens in resource-limited settings: evidence from routine clinical practice in Cameroon. *BMC Infect Dis* 2019;19:246.
- Edessa D, Sisay M, Asefa F. Second-Line HIV treatment failure in sub-Saharan Africa: a systematic review and meta-analysis. *PLoS One* 2019;14:e0220159.
- Brown JA, Ringera I, Luoga E, *et al*. Genotype-Informed versus empiric management of viremia (give move): study protocol of an open-label randomised clinical trial in children and adolescents living with HIV in Lesotho and Tanzania. *BMC Infect Dis* 2020;20:773.
- National AIDS Control Programme. *National guidelines for management of HIV and AIDS*. 181. 6th ed, 2017.
- Dorward J, Lessells R, Drain PK, *et al*. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. *Lancet HIV* 2018;5:e400–4.
- World Health Organization. WHO manual for HIV drug resistance testing using dried blood spot specimens, 2020. Available: <https://www.who.int/publications/i/item/9789240009424> [Accessed 30 Nov 2020].
- Tang MW, Liu TF, Shafer RW. The HIVdb system for HIV-1 genotypic resistance interpretation. *Intervirology* 2012;55:98–101.
- Ramadhani HO, Bartlett JA, Thielman NM, *et al*. Association of first-line and second-line antiretroviral therapy adherence. *Open Forum Infect Dis* 2014;1:ofu079.
- Shearer K, Evans D, Moyo F, *et al*. Treatment outcomes of over 1000 patients on second-line, protease inhibitor-based antiretroviral therapy from four public-sector HIV treatment facilities across Johannesburg, South Africa. *Trop Med Int Health* 2017;22:221–31.
- Siril HN, Kaaya SF, Smith Fawzi MK, *et al*. Clinical outcomes and loss to follow-up among people living with HIV participating in the NAMWEZA intervention in Dar es Salaam, Tanzania: a prospective cohort study. *AIDS Res Ther* 2017;14:18.
- Pennings PS. HIV drug resistance: problems and perspectives. *Infect Dis Rep* 2013;5:e5.
- Hosseinipour MC, Gupta RK, Van Zyl G, *et al*. Emergence of HIV drug resistance during first- and second-line antiretroviral therapy in resource-limited settings. *J Infect Dis* 2013;207(Suppl 2):S49–56.
- Matilda Ngarina CK, Karlsson K, Aboud S. Virologic and immunologic failure, drug resistance and mortality during the first 24 months postpartum among HIV-infected women initiated on antiretroviral therapy for life in the Mitra plus study, Dar ES Salaam, Tanzania. *BMC Infect Dis* 2015;15:173.
- Ekong E, Ndembu N, Okonkwo P, *et al*. Epidemiologic and viral predictors of antiretroviral drug resistance among persons living with HIV in a large treatment program in Nigeria. *AIDS Res Ther* 2020;17:7.
- Fokam J, Elat J-BN, Billong SC, *et al*. Monitoring HIV drug resistance early warning indicators in Cameroon: a study following the revised World Health organization recommendations. *PLoS One* 2015;10:e0129210.
- Rokx C, Schurink CAM, Boucher CAB, *et al*. Dolutegravir as maintenance monotherapy: first experiences in HIV-1 patients. *J Antimicrob Chemother* 2016;71:1632–6.
- Moreno M, Caballero E, Mateus RM, *et al*. HIV drug resistance in Africa: an emerging problem that deserves urgent attention. *AIDS* 2017;31:1637–9.
- Organization WH. *HIV drug resistance report 2019*, 2019.