Tuberculosis, HIV, and viral hepatitis diagnostics in eastern Europe and central Asia: high time for integrated and people-centred services

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Globally, high rates (and in the WHO European region an increasing prevalence) of co-infection with tuberculosis and HIV and HIV and hepatitis C virus exist. In eastern European and central Asian countries, the tuberculosis, HIV, and viral hepatitis programmes, including diagnostic services, are separate vertical structures. In this Personal View, we consider underlying reasons for the poor integration for these diseases, particularly in the WHO European region, and how to address this with an initial focus on diagnostic services. In part, this low integration has reflected different diagnostic development histories, global funding sources, and sample types used for diagnosis (eg, typically sputum for tuberculosis and blood for HIV and hepatitis C). Cooperation between services improved as patients with tuberculosis needed routine testing for HIV and vice versa, but financial, infection control, and logistical barriers remain. Multidisease diagnostic platforms exist, but to be used optimally, appropriate staff training and sensible understanding of different laboratory and infection control risks needs rapid implementation. Technically these ideas are all feasible. Poor coordination between these vertical systems remains unhelpful. There is a need to increase political and operational integration of diagnostic and treatment services and bring them closer to patients.

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Introduction

In the past 20 years rapid molecular tools have revolutionised the work of tuberculosis laboratories. Classic microbiology-based culture examinations of patient specimens and drug-susceptibility testing are increasingly replaced, at least in part, with rapid molecular tests, offering results in hours or days rather than weeks or months.[1–4] Understanding of how specific mutations in the *Mycobacterium tuberculosis* genome are related to drug resistance is rapidly increasing, and molecular detection of such resistance-predicting mutations is often used to rapidly detect drug-resistant tuberculosis[5–11] and potentially could be used to initiate personalised treatment regimens.[12] An additional added value of replacing conventional tuberculosis diagnostic methods, based on mycobacterial culture, to modern molecular assays, is that, although they still require training of laboratory staff, they permit tuberculosis diagnosis to take place in less specialised laboratories, closer to patients. A similar trend is seen in using PCR and sequencing-based technologies for detection of drug-resistant HIV.[13] Although a commercially available and automated diagnostic tool recommended by WHO, such as the GeneXpert system (Cepheid; Sunnyvale, CA, USA), has shown its applicability in a combined diagnostic landscape, the full role of sequencing-based technologies, increasingly used in characterisation of different infectious disease pathogens offers great opportunities in the near future. Next-generation sequencing (NGS), including both targeted sequencing and whole-genome sequencing (WGS), is becoming increasingly affordable and thus more widely used in, for example, the study of resistance mutations in viruses and bacteria such as *M tuberculosis*.[11,14–16] At present, for tuberculosis, reliable NGS approaches are confined to grown cultures but successful attempts have been made to do NGS on sputum specimens[17–19] or by using a targeted gene approach.[20]

Great progress has been achieved in HIV diagnostics. Nowadays, wider use of rapid HIV tests and confirmation of positive results with additional rapid ELISA confirmatory testing[21] is simpler, faster, and more accurate and cost-effective than before. Use of modern fourth-generation combined antigen and antibody tests can now increase the accuracy of HIV diagnosis and reduce the number of misdiagnosed patients within the so-called window period in HIV testing.[21]

With increasing access to effective treatment of hepatitis C globally, any simplification of diagnostic algorithms for the disease allows for more rapid implementation of national control programmes.[22,23]

Background and current situation

Global and European policy

The commitments contained in the UN General Assembly political declarations on the fights against tuberculosis[24] and HIV/AIDS,[25] and the globally endorsed End TB strategy,[26] the *Global Health Sector Strategy on HIV, 2016–2021*,[27] and the *Global Health Sector Strategy on Viral Hepatitis 2016–2021*,[28] collectively agreed on universal health coverage and collaboration between diverse stakeholders to achieve their objectives. The WHO European region has translated these goals into regional action plans for tuberculosis (for 2016–20),[29] for HIV[30] and for viral hepatitis,[31] which were endorsed at the 65th[32] and 66th[33] sessions of the Regional Committee for Europe.

Integrating programmes benefits patients by maximising available infrastructure and resources (including staff) and minimising diagnostic and therapeutic delay

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Panel: A good example of diagnostic service integration in Georgia

- Georgia provides an excellent example of what can be achieved when countries with vertical health systems for HIV, tuberculosis, and viral hepatitis management integrate to produce more people-centred health delivery models[46]
- During the past decade, access to full HIV and tuberculosis services (eg, screening, confirmation, treatment, and care) was guaranteed to patients in the capital city Tbilisi and in regional centres; the decentralisation was accelerated by an initiative to eliminate hepatitis C by 2020; this right to access has catalysed HIV and tuberculosis testing interventions with hepatitis C screening services at all different levels of health care[47]
- In 2018, a pilot project was started in the Samegrelo-Zemo Svaneti region to test the potential for integration of HCV, HIV, and tuberculosis screening services at the regional level and to engage primary health-care providers in detection and management of all three diseases (Khonelidze I, National Center for Disease Control and Public Health, Tbilisi, Georgia, personal communication)
- The project enabled both the development of a sustainable public-private partnership for effective integration of HIV, tuberculosis, and hepatitis C screening and early disease detection, and the decentralisation of diagnostic services (HIV and hepatitis C confirmation tests) at district level at non-specialised facilities
- Based on the promising results of the pilot, a national roll-out is planned for 2019–20 (Khonelidze I, National Center for Disease Control and Public Health, Tbilisi, Georgia, personal communication)
- A strong collaboration exists between tuberculosis and HIV services, including HIV screening of all people with active tuberculosis disease, tuberculosis case finding among people with HIV, and provision of treatment for both diseases; estimates of tuberculosis and HIV treatment coverage is over 90% and substantially exceeds global and European coverage.[47] For 2018, the global coverage was 48% and European 58%. The coverage for Georgia was 68%. Alternatively, the standard indicator is ART coverage among tuberculosis patients with known HIV-status who are HIV-positive. In 2018, the global coverage was 86% and European 73%. The coverage for Georgia in 2018 was 100%.[36]

for patients with multiple infections. Decreasing financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund) necessitates a maximising of efficiency especially for costly diagnostics and therapeutics. Nevertheless, despite the potential to improve diagnosis and treatment, HIV, tuberculosis, and viral hepatitis remain positioned as separate programmes.

Despite a substantial increase in access to antiretroviral therapy (ART), only 1·3 million of the 2·3 million people living with HIV in the WHO European region are on treatment.[34] HIV rates continue to increase in this region.[35] Tuberculosis remains one of the leading causes of death worldwide, and despite reductions, tuberculosis mortality among people living with HIV remains high;[35,36] high tuberculosis and HIV co-infection rates are still prevalent globally.[35–37] Viral hepatitis accounts for 171 000 deaths per year in the WHO European region[31] mainly due to hepatitis-related liver cirrhosis and cancer, attributable to hepatitis B and C virus infections.[31] Despite the high burden of chronic viral hepatitis, the response in most countries in the region has been inadequate.[28] Effectiveness of ART and anti-tuberculosis therapy is dependent on the ability to diagnose, treat, and monitor treatment outcomes. Additionally, WHO recommends the use of viral load testing for monitoring HIV ART.[38] Consequently, the need for timely viral load testing is increasing in low-resource, high-burden settings because more people are initiated on ART with the test-and-treat approach.[39] Scale-up of hepatitis C treatment has also increased the need for molecular diagnostic methods for hepatitis C virus infection confirmation and assessment of virological cure.[22] The need to diagnose HIV and tuberculosis rapidly,[40] together with high rates of loss to follow up, supports both integration and decentralising testing services in specific situations.[41–45]

Examples of these vertical structures are found worldwide, but particularly in the Eastern European and Central Asian (EECA) part of the WHO European region, where typically we find two scenarios depending on whether a patient presents initially to a tuberculosis or HIV service.

The diagnostic path of a patient with active tuberculosis

In many EECA countries with a high tuberculosis and HIV burden, all tuberculosis patients will be tested for HIV, hepatitis C, and hepatitis B in tuberculosis facilities. This approach is enshrined in local legislation and for tuberculosis patients, this screening will be free of charge. Blood samples collected in tuberculosis facilities will go to the AIDS centre for testing in their laboratories. Test results will be transferred to the tuberculosis facility and the doctor there will inform the patient about their HIV status. However, once a tuberculosis patient is identified as HIV positive, it is the patient's own responsibility to go to the AIDS centre. Although some countries have developed successful joint tuberculosis and HIV working services (panel), many have major challenges and gaps in HIV service delivery due to long delays before presentation to an AIDS specialist. Patients might avoid the AIDS centre because of stigma and try to hide their HIV status, and counselling, psychological, and community support is often missing within tuberculosis centres for people living with HIV.

Often, national guidance prevents smear-positive tuberculosis patients from attending AIDS centres on the basis of risk to infection control. In this case, the HIV specialist will visit the patient in the tuberculosis facility, but because of the unavailability of HIV specialists, initiation of ART is delayed.

The diagnostic path of a people living with HIV

In many EECA countries, legislation requires that all people living with HIV are tested for tuberculosis, hepatitis C virus, and hepatitis B virus in AIDS centres. The patient cannot be sent to a tuberculosis facility to prevent possible contact between immunocompromised patients and active tuberculosis patients. Screening is free of charge for people living with HIV.

Gaps exist in the tuberculosis service delivery from AIDS centres to people living with HIV. Patients are frequently delayed in seeing tuberculosis specialists because of restricted funding, too few specialists, and rapid increases in the number of people living with HIV. In addition, although some AIDS centres have the facilities to identify *M tuberculosis* (including GeneXpert machines), most AIDS centres collect sputum and send them to tuberculosis laboratories on the basis of local agreements. However, funding limitations often lead to delays in testing potential tuberculosis samples from AIDS centres. Both scenarios show the need and benefits of better integration of tuberculosis and HIV services and prospective integration of viral hepatitis services where relevant.

The current vertical design contributes to increased loss to follow-up of patients due to separate diagnostic and monitoring procedures, and the consequent burden for patients including the doubling of diagnostic visits and medical appointments with different specialists. Integrated models of care are thus highly desirable, as is decentralisation of services, making them available closer to patients.[26]

We address the inadequate integration of care for people with tuberculosis, HIV, and, hepatitis C particularly in low-income and middle-income, high disease-burden settings. We discuss barriers to better integration and opportunities to overcome the challenges.

Recommendations on rapid testing strategies

The new global 90-90-90 targets[48] call for 90% of all people with HIV to be diagnosed, 90% of people living with HIV to receive ART, and 90% of individuals on ART to have a suppressed viral load by 2020. WHO guidance[49] recommends expanding the setting where HIV testing is available and confirmation testing for HIV diagnosis, with swift linkage to care. Integration of HIV testing with testing services for other infections is clearly recommended in new European Centre for Disease Prevention and Control guidance around combined testing interventions for HIV, hepatitis B virus, and hepatitis C virus.[50] Expansion of this integrated approach to include tuberculosis has been restricted by the substantial differences in necessary training, equipment, and facilities required, despite recommendations for screening for tuberculosis in people living with HIV and vice versa.

Advances in point-of-care molecular diagnostics for tuberculosis, HIV, and hepatitis C

Since 2010, WHO has endorsed rapid automated molecular diagnostic technology using the GeneXpert platform (and the Xpert MTB/RIF assay [Cepheid]) for the detection of tuberculosis and rifampicin resistance directly from sputum.[51] The GeneXpert system can also be used for HIV-1 treatment monitoring Xpert HIV-1 Viral Load (Cepheid) and early infant diagnosis (eg, the Xpert HIV-1 Qual assay [Cepheid]) for measuring HIV-1 viral load in plasma, dried blood spots, or whole blood samples. Xpert HIV-1 Viral Load was prequalified by WHO in 2017 and Xpert HIV-1 Qual assay in 2016.[52,53] The Genexpert HIV Viral Load (Cepheid) has an estimated sensitivity of 40 copies per mL from plasma or serum samples and, overall, functions well compared with current reference tests.[54,55]

The Xpert HCV Viral Load (Cepheid) quantifies hepatitis C virus RNA in human serum or plasma and has an estimated sensitivity of 10 IU/mL with good correlation with reference techniques.[56] Therefore, the GeneXpert system can be used for confirmation of chronic infection (as for any other PCR-based test) and for the assessment of treatment outcome (ie, sustained virological response).

The GeneXpert system, even when implemented in low-income areas such as at the district health level in Zimbabwe, had the shortest overall median turnaround time for result delivery to the clinician (1 day) when compared with testing in reference laboratories (turnaround time of 17–125 days).[40] Similar results are found in middle-income and high-income countries.[57,58]

As other commercial multidisease platforms now exist (table), countries with existing (or planning on purchasing) multidisease platforms should consider collaborating to integrate HIV and hepatitis C viral load, or tuberculosis testing or both. This testing includes both high-throughput laboratory-based instruments for HIV viral load measurement and near point-of-care instruments, such as GeneXpert systems for HIV, hepatitis C virus, and tuberculosis.[23]

This array of available assays offers a range of possibilities for high-throughput and near-point-of-care diagnostics for tuberculosis, HIV, and hepatitis C. These new techniques also offer the potential of using more generalist rather than specialist staff.[60] The portability of point-of-care platforms might make it possible to decentralise first-line diagnosis and monitoring, taking services directly to affected communities, and enabling service delivery in proximity settings (eg, community centres or mobile units in outreach settings), and so maximising access.

	Manufacturer	HIV	Hepatitis C virus	Tuberculosis	Multidrug-resistant tuberculosis	Description
m2000 RealTime System	Abbott Laboratories (Chicago, IL, USA)	Yes	Yes	Yes	Yes	PCR-based platform
qTOWER3 system	Analytik Jena (Jena, Germany)	Yes	Yes	Yes	No	PCR-based platforms
GeneXpert System	Cepheid (Sunnyvale, CA, USA)	Yes	Yes	Yes	Yes	PCR-based platform
Cobas platforms	Roche (Basel, Switzerland)	Yes	Yes	Yes	No	PCR-based platforms
SaCycler-96	Sacace Biotechnologies (Como, Italy)	Yes	Yes	Yes	No	PCR-based platform
GeneXpert I	Cepheid (Sunnyvale, CA, USA)	Yes	Yes	Yes	Yes	Point-of-care or near-point-of-care device
SLAN	LG Life Sciences (Hongshi Tech, Shanghai, China)	No	Yes	Yes	No	PCR-based platforms
QIAsymphony SP/AS	QIAGEN (Venlo, Netherlands)	No	Yes	Yes	No	PCR-based platforms

Table: **Molecular multidisease nucleic acid testing platforms for at least two of HIV, hepatitis C, and tuberculosis[59]**

Public health and patient benefit of greater collaboration

The End TB strategy recognises the importance of collaboration between tuberculosis and HIV programmes.[26] Benefits of integration between programmes include: efficient use of resources currently allocated separately to programmes through sharing of staff expertise, health facilities, equipment and infrastructure; rapid and coordinated identification and management of patients with co-infections; and simplified, people-centred rather than disease-centred service delivery systems.

Integration with additional services, might increase both service uptake and retention for target populations. For example, co-infection with tuberculosis and HIV, or hepatitis C virus and HIV disproportionately affects key populations, such as people who inject drugs or patients residing in prisons. Because these people are less likely to use formal health settings, assuring timely access to other relevant health services, such as ART, opioid substitution treatment, and access to viral hepatitis diagnostic and therapeutic services, is crucial.[61]

Additionally, with the global increase in life expectancy[62,63] the burden of chronic disease, and the prevalence of multiple morbidities,[64] will increase. Wider integration might permit, in the longer term, the delivery of both infectious and chronic disease diagnostic and therapeutic services in more cost-effective ways.[65,66]

Challenges to integrating vertical programmes

EECA tuberculosis laboratory networks generally have a tiered structure, with microscopy and rapid molecular diagnostics such as GeneXpert platforms at the district level, culture and GeneXpert at the intermediate level, and culture and drug susceptibility testing with use of conventional and molecular genetic methods at the national or regional reference laboratory. The HIV programme has had a more centralised service by comparison. HIV laboratories at a district level are not integrated into primary health-care services and usually do not have GeneXpert or equivalent platforms. For these systems, in which samples are transported to regional and national laboratories, results take time to come back to clinicians. The situation is exacerbated by inadequate laboratory information management systems and less than timely communication between treating clinicians in the case of co-infections.

Technology has driven potential decentralisation furthest for HIV diagnosis where people can self-test in their own home using oral buccal swabs.[67] Confirmatory testing is still required, however.

Opportunities: use of multidisease diagnostic platforms

The GeneXpert tuberculosis assays, while considering appropriate biosafety considerations, can be successfully operated by staff with basic or less-specialist training.[60]

Testing with, for example, GeneXpert platforms, is possible in most health-care settings, although some additional resources and adaptation are required. For facilities with tuberculosis GeneXpert instruments and assays, modest upgrades to enable multiple disease testing might be required (eg, different cartridges or software, refrigerators for plasma sample storage, centrifuges) and protocols are available for this.

Taking advantage of existing GeneXpert equipment, especially at district and regional levels, can enable their wider use, maximise their effectiveness, and enable quicker delivery of not only tuberculosis test results, but also HIV-1 and hepatitis C diagnosis, viral load monitoring in people living with HIV, and early infant diagnosis of HIV-1. As novel hepatitis C virus treatments are highly effective, initial viral load monitoring would be needed but would not be essential longer term (as is the case in HIV).

In the last decade an increase in the provision of community and non-governmental organisation (NGO) services offering HIV, viral hepatitis, and other sexually transmitted infection testing has occurred, and evidence exists showing their ability to reach key populations and detect previously unknown HIV, hepatitis C, and

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hepatitis B infections.[49,50,68–70] Although most of these services use rapid serological tests and often do not have the equipment for more complex procedures, some have incorporated point-of-care platforms, which allow diagnosis of HIV and other infections.

The sharing of technological platforms will also facilitate implementation of modern diagnostic connectivity solutions leading to streamlining of record keeping of test results and better communication and follow-up.

Efficient use of restricted funding

The balance between disease-specific programmes and strategies, and the need for further integration and strengthening of health services, has received attention from the Global Fund not only at a strategic,[71] but also at an implementation level.[72]

Currently the Global Fund, which supports diagnostic activities in many countries, has requested that ministries of health shift from donor budget funding to state budget funding covering at least 30% of all activities and ideally 100% of costs through domestic funds by the end of 2020.[73] This change makes consideration of the value of integration of separate tuberculosis, HIV, and hepatitis C diagnostic services more crucial and multidisease diagnostic platforms make this possible.

Promoting change: the role of governments, donors, and international organisations

Political and donor support, and civil society advocacy for greater integration of diagnostic services for tuberculosis, HIV, and viral hepatitis are necessary. So far, contributions from governments, international NGOs, and public-private partnerships have improved access to the GeneXpert platforms following the WHO recommendation for their use in 2010, which led to a transformation of tuberculosis and rifampicin-resistance testing globally.[74]

Ministries of health are key for moving forward the integration of these services. However, political willingness needs to be supported and complemented by streamlined communication with donors, and funding strategies of national and international agencies need to be in line with this goal. Stimulating the development of solid investment cases and fostering the involvement of ministries of finance in the planning and analysis of integrated service delivery models might help systematic-level change because increasing effectiveness without increasing resource allocation is a rare opportunity.

Additionally, reduced requirement for external resources (by maximising the use of diagnostic equipment) within the national health systems will be an added benefit for countries and the people affected by these diseases.

Programme managers (and laboratory experts) have a key role in maximising patient outcomes and cost-effectiveness by deciding on placement of multidisease diagnostic platforms and determining testing volumes, reliable sample and result transport systems, and human resource capacity. For example, because of their experience of using GeneXpert platforms in tuberculosis services, HIV or hepatitis C viral load testing could be easily delegated to tuberculosis laboratory technicians with existing practical experience of Xpert MTB/RIF testing. This shared experience includes training on regular maintenance, troubleshooting, annual calibration, and replacement of modules.

Having a single, efficient sample transport system building on any existing well functioning in-country system would also be more beneficial than having completely parallel systems.

Conclusion

Evidence supports the feasibility of integrated diagnostic testing using multidisease diagnostic platforms within district and sub-district health facilities.[40] Improved access to optimised laboratory-based testing services would be mutually beneficial for tuberculosis, HIV, and hepatitis C programmes.

Contributors

The initial draft was prepared by MD, SE, GK, DS, and FD. The revised version was produced by FD. MD, and FD contributed equally to the Personal View. All remaining authors contributed equally to rewriting and producing the final draft.

Declaration of interests

We declare no competing interests.

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