# DRUG RESISTANCE RELATED TO AIDS, TUBERCULOSIS AND MALARIA IN THE AFRICAN REGION

Rufaro Chatora
Rui Gama Vaz
Bah Keita
Georges Alfred Ki-Zerbo
Assimawè Pana
Ibrahima Socé Fall
Nathan Bakyaita
Wilfred Nkhoma
Daniel Kibuga
Guy Michel Gershy-Damet

Division of Prevention and Control of AIDS, TB and Malaria
World Health Organization
Regional Office for Africa

Corresponding author:
Rufaro Chatora
Email: ChatoraR@afro.who.int

**With just 10% of the world population, sub-Saharan Africa has the highest burden of HIV/AIDS, tuberculosis and malaria in the world. Both access to and adequate utilization of effective treatment with quality-assured medicines are crucial for reducing the disease burden. However, efforts to improve access to treatment are hampered by the development of HIV, TB and malaria drug resistance. This is a result of genetic mutations and is a major threat to control of HIV/AIDS, TB and malaria.**

**HIV drug resistance can be minimized by good antiretroviral treatment (ART) programmes, removal of barriers to continuous access to ART and reduction of HIV transmission. Recent surveys conducted at antenatal clinics in several countries in the African Region estimated that HIV resistance to all drug classes is less than 5%. A global HIV drug resistance network established in 2001 supports countries in capacity building and guidance on standard procedures for monitoring HIV drug resistance.**

**Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are principally a result of inadequate or poorly administered treatment regimens. The new WHO Stop TB Strategy launched in 2006 identifies management of MDR-TB as a core component of TB control. The magnitude of MDR-TB in the African Region is still unknown. Since 2007, 33 countries notified MDR-TB cases, and eight reported at least one case of XDR-TB.**

**Following widespread resistance to chloroquine and sulphadoxine-pyrimethamine all malaria-endemic countries except two in the Region have changed the treatment policy to artemisinin-based combination therapy (ACT). The main method of monitoring antimalarial drug resistance is through therapeutic efficacy testing. To date there has been no confirmed resistance to ACTs in the African Region.**

**Given the emergence and spread of resistance to HIV, TB and malaria drugs, the purpose of this paper is to describe the issues and challenges and propose a way forward with regard to the prevention and control of such resistance.**

## RÉSUMÉ

Avec seulement 10% de la population mondiale, l'Afrique sub-saharienne est le pays le plus fortement accablé par le VIH / SIDA, la tuberculose et le paludisme dans le monde. Tant l'accès que l'utilisation adéquate de traitements efficaces utilisant des médicaments de qualité assurée sont essentiels pour réduire le poids de la maladie. Toutefois, les efforts pour améliorer l'accès au traitement sont entravés par l'évolution du VIH, de la tuberculose et par la résistance aux médicaments contre le paludisme. Ceci est le résultat de mutations génétiques et constitue une menace majeure pour le contrôle du VIH / SIDA, de la tuberculose et du paludisme.

La pharmaco-résistance du VIH peut être réduite en mettant en place de bons programmes de traitements antirétroviraux (TAR), en supprimant les obstacles pour avoir un accès permanent aux traitements antirétroviraux (TAR) et en réduisant la transmission du VIH. Dans plusieurs pays de la région africaine, des enquêtes récentes menées dans les dispensaires prénatals ont estimé que la résistance du VIH à toutes les classes de médicaments est inférieure à 5%. Un réseau global de pharmaco-résistance du VIH, créé en 2001, soutient les pays pour renforcer leurs capacités et leurs conseils par rapport aux procédures standard pour surveiller la pharmaco-résistance du VIH.

La tuberculose pharmaco-résistante (TB-PR) et la tuberculose ultra-pharmaco-résistante (TB-UPR) sont essentiellement la conséquence de traitements inadéquats ou mal administrés. La nouvelle stratégie de l'OMS "Stop à la tuberculose", lancée en 2006, identifie la gestion de la tuberculose pharmaco-résistante (TB-PR) comme étant un élément central de la lutte antituberculeuse. L'ampleur de la tuberculose pharmaco-résistance (TB-PR) dans la région africaine est encore inconnue. Depuis 2007, 33 pays ont notifié des cas de tuberculoses pharmaco-résistantes (TB-PR), et 6 ont signalé au moins un cas de tuberculose ultra pharmaco-résistante (TB-UPR).

Après une résistance généralisée à la chloroquine et à la sulfadoxine-pyriméthamine, tous les pays atteints de malaria endémique, sauf deux dans la région africaine, ont changé la politique de traitement pour une thérapie combinée à base d'artémisinine (TCA). La principale méthode de surveillance de la résistance aux antipaludiques se fait par le biais de tests d'efficacité thérapeutiques. À ce jour, dans la région africaine, il n'y a eu aucune résistance confirmée aux thérapies combinées à base d'artémisinine (TCA).

Etant donné l'émergence et la propagation de la résistance aux médicaments contre le VIH, la tuberculose et le paludisme, le but de cet article est de décrire les enjeux et les défis ainsi que de proposer une voie à suivre en ce qui concerne la prévention et le contrôle d'une telle résistance.

## SUMÁRIO

Com apenas 10% da população mundial, a África subsariana apresenta o maior fardo relacionado com o VIH/SIDA, tuberculose e malária em todo o mundo. Tanto o acesso, como a utilização adequada de tratamentos eficazes com medicamentos de qualidade garantida são cruciais para a redução do fardo associado a estas doenças. No entanto, os esforços para melhorar o acesso ao tratamento têm sido dificultados pelo desenvolvimento de resistência aos medicamentos contra a SIDA,, a tuberculose (TB) e malária. Isso é devido a mutações genéticas e representa uma ameaça grave para o controlo do VIH/ SIDA, TB e malária.

A resistência aos medicamentos contra a SIDA pode ser reduzida através de bons programas de tratamento anti-retro virais (ART), a remoção das barreiras ao acesso contínuado aos ART e a redução da transmissão do VIH. Estudos recentes realizados em clínicas pré-natais em diversos países da Região Africana estima-se que a resistência a todas as classes de medicamentos é inferior a 5%. Uma rede mundial relacionada com a resistência a medicamentos, estabelecida em 2001, ajuda países a criar capacidade e a proporciona orientação relativa a processos estandardizados na monitorização da resistência a medicamentos contra a SIDA.

A tuberculose multi-resistente (MDR-TB), a tuberculose extensivamente resistente (XDR-TB) são sobretudo o resultado de tratamentos inadequados ou mal administrados. A nova estratégia da OMS para travar a tuberculose (WHO Stop TB Strategy) publicada em 2006, identifica a gestão da MDR-TB como a componente central do controlo da TB. A dimensão da MDR-TB na Região Africana continua desconhecida. Em 2007, 27 países anunciaram casos de MDR-TB e seis comunicaram pelo menos um caso de XDR-TB.WRITE Desde 2007, 33 países anunciaram casos de MDR-TB e 8 comunicaram pelo menos um caso de XDR-TB.

A seguir à resistência generalizada à cloroquina e sulfadoxina-pirimetamina todos os países com malária endémica com a excepção de dois países na Região alteraram a sua política de tratamento a favor de uma terapia combinada à base de artemisinina (ACT). O método principal na monitorização da resistência a medicamentos contra a malária é a realização de ensaios rigorosos relativos à eficácia terapêutica. Até à data não foi confirmada uma resistência à ACTs na Região Africana.

Face ao aparecimento e à propagação da resistência aos medicamentos contra a SIDA, TB e malária, o objectivo deste relatório é a descrição das questões e dos desafios e propor um caminho para prevenir e controlar estas resistências.

GIVEN THE EMERGENCE AND SPREAD OF RESISTANCE TO HIV, TB AND MALARIA DRUGS, THE PURPOSE OF THIS PAPER IS TO DESCRIBE THE ISSUES AND CHALLENGES AND PROPOSE A WAY FORWARD WITH REGARD TO THE PREVENTION AND CONTROL OF SUCH RESISTANCE.

**With just 10% of the world population, sub-Saharan Africa has the highest burden of HIV/AIDS, tuberculosis and malaria in the world. In 2003, ministers of health of the 46 countries of the African Region adopted a resolution on scaling up of interventions against HIV/AIDS, tuberculosis and malaria. The resolution recognized that both access to and adequate utilization of effective treatment with quality-assured medicines are crucial for reducing the disease burden.**

**However, efforts to improve access to treatment are hampered by the development of HIV, TB and malaria drug resistance. Drug resistance is defined as the ability of an infectious agent to survive or multiply despite the administration and absorption of medicine given in doses equal to or higher than those usually recommended but within tolerance of the subject. This is a result of genetic mutations and is a major threat to control of HIV/AIDS, TB and malaria.**

## METHODS

**The information presented in this paper was compiled from literature search and desk review of published and unpublished papers as well as technical and field reports on drug resistance from countries. The paper has been reviewed by a technical panel at the WHO Regional Office for Africa; it was also presented to Ministers of Health of the WHO African Region at their 59th session of the Regional Committee.**

The need for lifelong antiretroviral treatment (ART), coupled with the high HIV replication and mutation rates, means that resistance will emerge even among appropriately treated, compliant individuals. However, HIV drug resistance can be minimized by good ART programmes, removal of barriers to continuous access to ART and reduction of HIV transmission.[2]

HIV drug resistance assessment is primarily through monitoring of early warning indicators at ART sites. HIV drug resistance surveys are also performed in geographic areas where ART has been widespread for more than 3 years. Recent surveys conducted at antenatal clinics in several countries in the African Region estimated that HIV resistance to all drug classes is less than 5%.[4,5,6,7] A global HIV drug resistance network established in 2001 supports countries in capacity building and guidance on standard procedures for monitoring HIV drug resistance.[8]

Multidrug-resistant TB (MDR-TB) is defined as tuberculosis caused by organisms that are resistant to at least isoniazid and rifampicin. Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB that is also resistant to any one of the fluoroquinolones and to at least one of three injectable second-line medicines (amikacin, capreomycin or kanamycin).[9] MDR-TB and XDR-TB are principally a result of inadequate or poorly administered treatment regimens.

The new WHO Stop TB Strategy launched in 2006 identifies management of MDR-TB as a core component of TB control. The magnitude of MDR-TB in the African Region is still unknown. Since 2007, 33 countries notified MDR-TB cases, and eight reported at least one case of XDR-TB.

Following widespread resistance to chloroquine and sulphadoxine-pyrimethamine all malaria-endemic countries except two in the Region have changed the treatment policy to artemisinin-based combination therapy (ACT). Since 1997, countries in the Region have established six subregional antimalarial drug resistance networks that have provided a forum for information sharing, capacity building and the development of new treatment policies (ACTs) across the Region.

The main method of monitoring antimalarial drug resistance is through therapeutic efficacy testing. To date there has been no confirmed resistance to ACTs in the African Region. However,

since 2003, evidence has been accumulating that ACTs are less effective against Plasmodium falciparum on the Cambodia-Thailand border.[10,11]

Given the emergence and spread of resistance to HIV, TB and malaria drugs, the purpose of this paper is to describe the issues and challenges and propose a way forward with regard to the prevention and control of such resistance.

## ISSUES

The use of combination therapy is recommended in the treatment of AIDS, TB and malaria as one of the approaches to prevent the development of drug-resistant strains. ART regimens should include potent combinations of at least two classes of ARV drugs. Tuberculosis treatment regimens have always been based on a combination of medicines. The first-line treatment for malaria is now artemisinin-based combination therapies (ACTs) which is also a combination of medicines. However, off-the-counter sales, inappropriate prescription of medicines by inadequately trained or supervised health workers coupled with poor compliance by patients are still major challenges in the African Region.

Prolonging the useful therapeutic life of AIDS, TB and malaria drugs through rational use of medicines while ensuring complete patient treatment (or, in the case of HIV, life-long treatment) is a major issue. Poor procurement and supply management systems leading to stock-outs and sometimes use of expired medicines increase the probability of developing drug-resistant strains of HIV, TB and malaria. Poor compliance with treatment regimens and limited availability of support systems for patients also contribute to the emergence of drug resistance. Similarly, there is concern about increased infiltration of markets by substandard and fake medications against life-threatening diseases in developing countries.[12]

Owing to their high cost and limited global supply, second-line medicines for the treatment of MDR-TB and XDR-TB are not readily available in countries. Second-line TB medicines are less effective and more toxic than first-line medicines and cost 3 to 20 times more – a huge financial burden that most countries cannot afford. Similarly, second-line antiretroviral medicines are more expensive. Of the 33 countries reporting any MDR-TB cases since 2007, only 20 were known to have an MDR-TB treatment programme. Even where treatment programmes exist, not all confirmed cases are accessing treatment.

Good laboratory services are essential for confirming diagnosis, monitoring treatment outcomes and guiding decisions to change to second-line treatment. Rapid diagnostic tests (RDTs) in general have increased opportunities for case confirmation and promotion of rational prescription. RDTs are now readily available for HIV and malaria. New technologies such as liquid culture media are being introduced for TB; many reduce the time required for drug susceptibility testing. Laboratory capacity is, however, still limited in the Region. For HIV, universal availability and use of appropriate, affordable CD4 testing and HIV viral-load testing are needed to monitor ART and to limit emergence of resistance. However, routine measurement of CD4 counts and HIV viral loads for patients on ART is still limited in many countries in the Region.[13,14]

For TB, most countries have limited national laboratory capacity for acid-fast bacilli (AFB) culture and drug susceptibility testing and have to send samples to laboratories in other countries or to supra-national laboratories. Transfer of samples across borders requires compliance with stringent regulations. Of the 25 global supra-national TB reference laboratories, only two are in the African Region, and

these are already overloaded. HIV drug-resistance testing is not recommended for routine clinical ART management in the Region; the ResNet network of accredited genotyping laboratories in the Region, with additional support from specialist laboratories, is adequate for current surveillance needs.

In most TB control programmes, there is a general lack of infection control at community and health facility level that is necessary for reducing transmission of TB, MDR-TB and XDR-TB. This is a result of the introduction of short-course chemotherapy as the treatment of choice in 1993 which deviated from the previous policy of isolating TB patients during treatment. The recent upsurge of MDR-TB and XDR-TB has, however, raised awareness about the need to reintroduce stringent infection control measures to break transmission of all forms of TB in communities and health-care settings.

Although there has been an increase in financial resources for the control of HIV/AIDS, TB and malaria, these resources cannot readily be used for the development of infrastructure that is necessary for drug resistance monitoring. Some equipment and reagents for drug resistance monitoring are expensive to purchase and maintain.

# THE WAY FORWARD

**Most of the issues related to the widespread development of drug resistance to HIV/AIDS, TB and malaria are due to health system challenges. These include among others, policies and strategies, coordination mechanisms, human resources, laboratory infrastructure, procurement and supply management including logistics, monitoring and evaluation, infection control as well as research and resources mobilization. These challenges must be addressed before the situation worsens. Countries should thus take the following concrete steps to prevent and control of drug resistance related to AIDS, tuberculosis and malaria.**

## ➡ DEVELOP AND IMPLEMENT POLICIES AND STRATEGIES THAT IMPROVE ACCESS TO CORRECT DIAGNOSIS AND EARLY EFFECTIVE TREATMENT

An important first step is to develop or strengthen clear policies and strategies for management of HIV/AIDS, TB and malaria to address issues such as affordability, access and quality of services while ensuring full community engagement in the process. Policy must elaborate clear diagnostic and treatment guidelines which are user-friendly and consider the different types of service providers. Guidelines must be updated regularly, ensuring clear criteria for changing from first-line medicines to second-line or higher level regimens. Guidelines should also address issues surrounding rational use of medicines, pharmacovigilance, drug resistance monitoring and quality assurance. Monitoring of patient compliance should also be ensured at all levels through patient education and training of service providers.

## ➡ DEVELOP HUMAN RESOURCE CAPACITY FOR PREVENTION AND MANAGEMENT OF DRUG RESISTANCE

Countries should ensure that all relevant health workers are aware of the factors related to development and management of drug resistance related to AIDS, TB and malaria. There is need to train service providers in the rational use of drugs as well as in the recognition and management of drug side-effects in order to ensure adherence of patients to treatment.

## ➡ STRENGTHEN NATIONAL AND SUBNATIONAL HEALTH LABORATORY NETWORKS

Ideally, the national laboratory network should have a pyramidal structure. For example, for TB, there should be one AFB microscopy laboratory serving a population of approximately 50 000. There

should also be one AFB culture laboratory per 5 million population and at least one national reference laboratory with drug sensitivity testing capability per country.

### ➡ ESTABLISH AND SUSTAIN SUBREGIONAL NETWORKS FOR DRUG RESISTANCE MONITORING

Subregional networks can serve as hubs for capacity building and technical assistance for drug susceptibility testing as well as platforms for strategic information sharing across countries for decision-making. They can also provide backup support to the national laboratory networks and quality assurance services. Furthermore, they should participate in drug resistance monitoring and surveillance programmes. Collaboration with centres of excellence should be encouraged. While drug resistance networks are operational for HIV/AIDS[15] and TB, there is need to revive the dormant malaria networks.

### ➡ STRENGTHEN PROCUREMENT AND SUPPLY OF HIV/AIDS, TUBERCULOSIS AND MALARIA MEDICINES

Countries need to strengthen their procurement and supply chain management systems to ensure uninterrupted availability of good quality, affordable medicines and commodities for prevention and control of HIV/AIDS, tuberculosis and malaria. Appropriate implementation of activities on quantification and forecasting, acquisition, stock and logistics management, distribution, quality assurance, appropriate use, pharmacovigilance, information system management and reinforcement of regulations to prevent proliferation of counterfeit medicines, will contribute to reducing the risk of drug resistance.

### ➡ SET UP DRUG RESISTANCE AND DRUG EFFICACY MONITORING SYSTEMS

Regular monitoring of resistance to TB medicines should be conducted as an integral part of routine surveillance. All cases identified should be reported; cases of MDR-TB and XDR-TB should be notified. With HIV representative surveys on a population level are recommended as part of routine surveillance. For malaria, therapeutic efficacy tests of first- and second-line medicines should be conducted at designated sentinel sites.

### ➡ IMPLEMENT ADMINISTRATIVE, ENVIRONMENTAL AND PERSONAL PROTECTION INFECTION CONTROL MEASURES FOR MDR- AND XDR-TB

It is necessary to institute administrative, environmental and personal protection and integrated infection control

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measures in order to minimize transmission to vulnerable groups such as health-care workers, family members and persons living with HIV/AIDS. Administrative measures include putting in place and implementing an infection control policy which provides for training of staff, education of patients and public, isolation of patients and use of respirators. Environmental controls include ventilation, filtration or ultraviolet germicidal irradiation.

### ➡ ADVOCATE FOR RESEARCH AND DEVELOPMENT OF NEW DIAGNOSTIC TOOLS AND MEDICINES

Operational research on specimen collection and transportation in resource-limited countries is required. Operational research is also required on adaptation of the directly-observed treatment short course to the challenges of MDR-TB and XDR-TB. For HIV, laboratory tests to monitor adverse events and ART failure would do more to limit resistance than access to resistance testing. New point-of-care technology for CD4 counts and viral loads is an urgent requirement. Capacity for conducting clinical trials for new drugs should be improved in the Region.

### ➡ MOBILIZE FINANCIAL RESOURCES FOR SUPPORTING IMPLEMENTATION OF DRUG RESISTANCE ACTIONS IN THE CONTEXT OF HEALTH SYSTEM STRENGTHENING

Countries should make provision in their national health budgets for funds to support activities for prevention, control and monitoring of drug resistance. Countries should also mobilize additional resources from global initiatives such as the Global Fund to Fight AIDS, Tuberculosis and Malaria; the President's Emergency Plan for AIDS Relief (United States); the US President's Malaria Initiative; and from the Bill and Melinda Gates Foundation and the World Bank. Funds mobilized from other partners would help strengthen health systems as well in order to address the emergence of drug resistance.

To address this situation, development partners should continue to provide technical support to countries, advocate for more resources and long-term international support, and monitor the progress in implementing interventions that aim to prevent and control drug resistance related to AIDS, tuberculosis and malaria.

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