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Access to experimental medicines for TB: ethical and human rights considerations

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SUMMARY

The revised edition of the WHO's *Ethics Guidance for the Implementation of the TB Strategy* has added a new chapter on compassionate use (CU) and expanded access (EA) to TB drugs. CU and EA programmes authorise access to drugs that have not yet received marketing approval outside of clinical trials. They are aimed at allowing researchers access to investigational drugs in the absence of complete evidence of efficacy and safety to patients with multidrug-resistant (MDR) or rifampicin-resistant TB (RR-TB) when no other treatment options are available. In doing so, the guidance acknowledged the urgent necessity to offer these patients all possible treatments in respect of considerations of justice, human rights, human dignity, autonomy of the individual and protection of the community. Regulators are in general willing to accept a higher level of uncertainty in the risk-benefit assessment of medicines for life-threatening diseases when there is an unmet medical need. This attests to a paradigm change, which this article argues should also apply to allow for effective access to experimental TB medicines. Furthermore, in this article, we analyse the challenges connected to the establishment of a secure and effective regime of access to experimental drugs in the context of MDR/RR-TB as well as the ethical principles and human rights arguments in favour of the development of such programmes.

KEY WORDS: compassionate use; human rights; ethics guidance

THE WORLD HEALTH ORGANIZATION (WHO) reiterated in its 2017 revised edition of the *Ethics Guidance for the Implementation of the TB Strategy* its encouragement for the development of compassionate use (CU) programmes. This allows for the exceptional use, under strict surveillance, of TB 'medicines under development' (or experimental medicines) that could potentially be effective or lifesaving for patients for whom all other treatments have failed or are not viable due to side effects.[1] There is no universal definition of CU programmes. Following the restrictive definition adopted by the WHO, CU programmes authorise access outside of clinical trials to drugs that are at the last stages of development and have not yet received marketing approval.[2,3] The WHO also differentiates between two types of programmes: CU programmes are those that enable the physician to request a medicine for a specific patient, whereas expanded access (EA) programmes are designed for a group of patients, usually under clinical research settings. The WHO's encouragement of the development of such programmes is principally motivated by two interconnected factors: the constant increase in the number of patients in need of new treatments and the high uncertainty as to when new drugs will become available.

In 2016, an estimated 600 000 patients developed MDR/RR-TB. Of these, approximately 20% had isoniazid-susceptible TB (RR-TB), and 80% had multidrug-resistant TB (MDR-TB).[4] While treatment options for drug-susceptible TB have been limited for decades, they can achieve success rates higher than 85%. MDR/RR-TB, on the other hand, is far more difficult and expensive to treat, with patients often having to undergo long and complicated treatment regimens, with drugs which are less efficacious and more toxic that have severe side effects and far higher mortality rates.[4]

The five major first-line TB medicines were discovered between 1943 (streptomycin) and 1963 (rifampicin).[5,6] Since then, research for TB agents has stalled and only two drugs—bedaquiline and delamanid—have become available for the treatment of MDR/RR-TB.[7] With 17 new drugs currently in clinical trials,[1] for the first time in decades there are

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multiple TB drugs in the development pipeline.[8,9] Nevertheless, it remains uncertain whether these drugs will pass through clinical trials and be available in a timely manner for patients in need.

Before a drug can be marketed, regulatory approval regimes, introduced to protect patients against dangerous medicinal products, normally require that clinical trials must have been conducted to control the efficacy, safety and pharmacological quality of the drug. Indeed, ineffective, poor quality or harmful medicines can cause therapeutic failure, exacerbation of disease, resistance of microbes to medicines and even death.[10] However, the protection resulting from the implementation of regulatory approval regimes is of little comfort to patients with drug resistance and for whom current therapeutic approaches are limited. For these patients, access to an experimental drug may be the only hope of recovery.

The WHO ethics guidance acknowledges the need to offer patients all possible treatments in respect of considerations of dignity and individual autonomy. According to the guidance, as a matter of their dignity, each patient's life should be protected using all possible treatments, including those not yet approved, registered or fully tested. Respecting patients' autonomy means allowing patients to choose for themselves, on an individual basis, whether they want to take on the risks associated with late-stage experimental treatments.[1] Moreover, considerations of social justice, equity and the protection of public health, key values underpinning the guidance, also strengthen the case for CU/EA. Indeed, as TB disproportionately affects poor communities[11] and drug-resistant strains typically develop in settings with weak healthcare systems due to ineffective treatment and a lack of supportive measures for treatment adherence, MDR/RR-TB is, to a large extent, socially determined by poverty and failures in health systems. Second, because TB and MDR/RR-TB have, since the mid-twentieth century, primarily affected poor communities and poor countries, there has been little incentive for the pharmaceutical industry to develop new drugs. Both the epidemiology of MDR/RR-TB and the scarcity of treatment options are therefore to a significant extent caused by social inequities. It follows therefore that, as a matter of equity and social justice, governments and product developers and their donors, when applicable, have an ethical obligation to provide the option of experimental treatments to MDR/RR-TB patients. Furthermore, the WHO ethics guidance itself states: "[h]uman rights are a concrete legal expression of a certain set of ethical values, including human dignity, equality, non-discrimination, participation, solidarity and accountability".[1]

In this article, we discuss these considerations with reference to international human rights law, particularly the right to health, and analyse the impact these considerations have already had on the standards developed for the marketing of drugs around the world. We argue that providing access to such programmes for people with MDR-/RR-TB is a requirement under international human rights law.

HUMAN RIGHTS ARGUMENTS IN FAVOUR OF PROVIDING ACCESS TO EXPERIMENTAL DRUGS TO MDR/RR-TB PATIENTS

Until recently, the human rights discussion concerning access to experimental drugs was conducted with regard to the right to privacy, as guaranteed by Article 17 of the International Covenant on Civil and Political Rights (ICCPR) and Article 8 of the European Convention on Human Rights (ECHR). The right to privacy protects matters of a confidential nature as well as the freedom to live as one chooses; private choices regarding sexual orientation or other such intimate decisions are therefore protected.[12,13] This right is the basis for requiring consent to medical treatment, as well as the right to refuse treatment.[14] Consequently, the duty to ensure free and informed choices might also include choosing an experimental treatment.

This interpretation has been partly confirmed within the European system of human rights protection. According to the European Court of Human Rights (ECtHR) and the former European Commission of Human Rights, the right to private and family life protects the physical integrity of patients and implies an inviolable right to decide what can be done to one's body. The refusal of medical treatment, even in the case of a minor interference, falls under, and is protected by, this right,[15] which must also be respected in life-threatening cases. Thus, in the case *Horoz v. Turkey*, the Court ruled that the State, which respected the choice of a detainee to refuse any medical intervention, had not violated its obligations under the European Convention on Human Rights. In this case, the detainee died in prison after going on a hunger strike.[16]

This said, there are no clear judicial decisions at the international or regional level concerning whether the right to decide what can be done to one's health and body might also include a right to have access to experimental medicine. National courts in the United States, United Kingdom and Colombia have had the opportunity to pronounce themselves on this question—to date their answers have been inconclusive. Whereas the Colombian Constitutional Court and the High Court of Justice of England and Wales recognised a right to experimental medicines in the case of life-threatening diseases on the basis of the principle of the respect for personal autonomy where there are no alternative treatments,[17,18] courts in the United States have ruled that no constitutional right of access exists in these circumstances.[19,20]

A human rights argument in favour of access to experimental drugs should therefore combine the right to privacy with the right to health guaranteed under international human rights law and more particularly by Article 12 of the International Covenant on Economic, Social and Cultural Rights (ICESCR).[21] It should also be noted that the right to life, as well as the right to enjoy the benefits of scientific progress, also guaranteed under international human rights law,[22] might provide possible new avenues for reflection. However, first, the right to life has never been interpreted as imposing a positive obligation for the state to authorise access to unauthorised medicines. On the contrary, in the ECtHR's 2012 decision *Hristozov* concerning access to experimental medicines in the case of terminally ill cancer patients, the court refused to confront the contested legislation with Article 2 guaranteeing the right to life, considering that this article "cannot be interpreted as requiring access to unauthorized [medicines] to be regulated in a particular way".[23] Second, it is generally accepted that the right to enjoy the benefits of scientific progress' normative content requires development[24–26] and, as such, the right to health constitutes a more useful approach for articulating a human rights argument for such access.

The normative content of the right to health, as articulated by the UN Committee on Economic, Social and Cultural Rights (CESCR) in its general comment N° 14,[27] reinforces the ethical arguments mentioned in the WHO's ethics guidance. This right not only contains freedoms, such as the right to control one's health and body, but also entitlements, such as the "right to the enjoyment of facilities, goods, services and conditions necessary for the realisation of the highest attainable standard of health".[27] It protects patients' autonomy and dignity and contains the right to prevention, as well as the right to treatment and control of diseases. It therefore imposes a core obligation on states parties to take measures to prevent, treat and control epidemic and endemic diseases, and implies that patients should have access to CU programmes under certain circumstances.[27]

In these contexts, medicines are a central element of the right to health as they are part of the tools used for the prevention, treatment and control of epidemic, occupational and other diseases.[28] The UN's human rights bodies have affirmed this at the international level on numerous occasions. For example, the UN Commission on Human Rights explicitly acknowledged in 2004 that "prevention and comprehensive care and support, including treatment and access to medication for those infected and affected by pandemics such as HIV/AIDS, tuberculosis and malaria are inseparable elements of an effective response and must be integrated into a comprehensive approach to respond to such pandemics".[29] In its resolution adopted in 2009, the UN Human Rights Council considered, moreover, that access to medicines in such cases required States to ensure that appropriate medicines were available, accessible, culturally acceptable, and of good quality.[30]

As such, international human rights law does not precisely define what medicines are considered relevant and appropriate in this context. The Committee on economic, social and cultural rights solely states in its General comment on the right to health that health goods must "be scientifically and medically appropriate", which "requires, inter alia...scientifically approved and unexpired drugs".[27] The question therefore remains: how to define 'scientifically approved'. So far, this has been done on the basis of receipt of marketing approval, attributed on the basis of a standardly accepted risk-benefit ratio. However, recent developments show that this balance has shifted in the case of life-threatening diseases and communicable diseases that constitute a global public health threat.

RECOGNISING A PARADIGM CHANGE IN THE REGULATION OF ACCESS TO PHARMACEUTICALS: ARGUMENTS IN FAVOUR OF COMPASSIONATE USE PROGRAMMES FOR PATIENTS WITH MDR/RR-TB

It has increasingly been recognised that, in the case of life-threatening diseases and communicable diseases that constitute a global public health threat, regulatory authorities should refer to different standards than those traditionally used to allow access to experimental drugs. At the national and international level, regulatory authorities and UN organs have already accepted a paradigm change in the evaluation of quality and the risk-benefit analysis of programs allowing access to experimental drugs. These arguments should apply to cases of MDR/RR-TB.

National regulation and compassionate use programmes

At the national level, the legislative frameworks authorising CU attest to the emergence of a new paradigm: the severity of diseases, the absence of appropriate medicinal therapies and the urgency to bring new drugs to the market may justify the use of experimental drugs before or during the last phase of clinical trials. This new paradigm is the result of the AIDS tragedy and the tremendous pressure exercised by civil society to protect patients' rights.

This movement has resulted in particular in the transformation of the practices surrounding the marketing authorization of medicines.[31,32] In order to respond to the specific needs of patients with severe conditions and no access to therapeutic options, many countries have progressively allowed excep-

tions. The first legislative framework authorising access to experimental medicines was adopted in 1987 in the United States.[33] In the European Union (EU), similar measures were passed in 2001[34] and 2004.[35]

More recently, similar considerations justified the development in several countries of accelerated approval procedures that allow access to medicines at Phase II of their development, and which complete the range of procedures available authorising access to promising new drugs. Accelerated approval strategies are commonly granted on the basis of a corroborated positive effect on a specific surrogate endpoint that is thought reasonably likely to predict clinical benefit. Their double objective is to offer access to experimental treatments to patients with serious or immediately life-threatening diseases and to collect reliable data on safety and efficacy for the development of new drugs for marketing application. This second element is necessary to satisfy the requirement imposed on the sponsor to conduct post-approval clinical studies demonstrating the effect of the drug on a clinical outcome. Accelerated approval measures were adopted in 1992 in the United States as part of the Prescription Drug User Fee Act, and also in the EU in 2004[35] (so-called conditional early access procedures). They have already been used for the approval of the most recently developed anti-TB drugs, bedaquiline[36,37] and delaminid.[38]

Current international practices suggesting a new paradigm for the access to experimental medicines under certain circumstances

At the international level, a comparable change of paradigm in the specific case of communicable diseases that pose a threat to global public health has been confirmed recently with regard to the Ebola crisis and TB.

The first occasion concerns the 2014 Ebola outbreak in West Africa and the issue of access to experimental medicines that had shown promising results in the laboratory and in animal models. The debate about the use of experimental drugs erupted after two US health workers received the drug ZMapp (Mapp Biopharmaceutical, San Diego, CA, USA), produced by a biopharmaceutical laboratory based in California, which had not yet been evaluated in clinical trials. The question of access was discussed by an ethics advisory committee constituted by the WHO with the goal of giving its opinion on the ethical issues surrounding the usage of experimental drugs at this stage of the Ebola outbreak. The panel came to the conclusion that the exceptional situation of the Ebola outbreak created an ethical imperative to offer available medical interventions to persons already infected with the virus.[39] The panel also insisted on the necessity to conduct clinical tests simultaneously in order to gather empirical data on safety and efficacy. The WHO has endorsed this opinion and developed guidance materials in order to assist States and relevant partners with regard to the use of available therapies and vaccines.[40]

The opinion on the use of experimental medicines at a pre-clinical stage of development in the Ebola case was conceived for an extreme situation. Because of the particularities of the disease and the situation (sporadic disease, outbreak in countries with weak health systems, high lethality and extreme difficulties in conducting traditional clinical trials under these circumstances), collecting the normally required safety data was extremely difficult during the Ebola outbreak. However, it confirmed a broad consensus that should also concern other epidemics despite differences in the particularities of the diseases: that national regulatory frameworks and standards of safety and efficacy have to be adapted in the case of epidemics and pandemics that represent a major public health threat.

This consensus is now also emerging for TB. In 2015, the WHO included the recently developed anti-TB medicines for drug-resistant strains (delamanid and bedaquiline) in its Model List of Essential Medicines, despite the absence of complete evidence of efficacy and safety. These drugs have only received early and conditional approvals—and are therefore more secure than experimental medicines for Ebola. Besides technical considerations, the WHO Expert Committee's decision was also made in view of the high mortality rate of untreated TB, the strong side effects of existing medicines and many patients' absence of real therapeutic alternatives.[41] However, central to the decision was also the threat MDR/RR-TB poses to global public health. In fact, TB was declared a global epidemic by the WHO in 1993 and MDR/RR-TB is considered a global public health threat.[42,43] The existence of this threat therefore justifies broader access to medicines while under strict control and supervision.

CONCLUSION

States parties' core obligations under the ICESCR for the prevention and control of epidemic and endemic diseases should include access to experimental drugs for MDR/RR-TB or extensively drug-resistant TB (XDR-TB). By providing access to experimental drugs to people for whom there are no alternative medical therapies, these programmes offer an alternative, as well as a last chance to those in need of treatment, considerably reinforcing their individual rights. Furthermore, as promising experimental medicines constitute an additional means to help interrupt the transmission of the disease and therefore, eventually, to protect the entire population against

the propagation of the disease,[44] providing access to medicines which have not yet been fully authorised does not undermine the public interest. As such, they should also be added to the list of non-coercive measures that must be proposed to patients in accordance with ethical and human rights standards before exceptional measures such as isolation or detention can be considered.[45]

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RÉSUMÉ

L'édition révisée des *Orientations éthiques pour la mise en œuvre de la stratégie visant à mettre un terme à la tuberculose* (TB) contient un chapitre supplémentaire consacré à l'usage compassionnel (CU) et à l'accès élargi (EA) aux médicaments contre la TB. Les programmes de CU et d'EA autorisent l'accès, en dehors des essais cliniques, à des médicaments qui n'ont pas encore reçu d'autorisation de mise sur le marché. Ils visent à autoriser les docteurs à mettre des médicaments non autorisés, en l'absence de preuve absolue de leur efficacité et de leur sécurité, à la disposition de patients atteints de la tuberculose multirésistante (MDR-TB) ou résistante à la rifampicine (RR-TB), quand aucune autre option thérapeutique n'est disponible. Ce faisant, les Orientations éthiques soulignent l'impérative nécessité d'offrir un traitement à ces patients en respectant les principes de justice, de respect des droits humains, de dignité humaine, d'autonomie de l'individu et de protection de la communauté. Lorsqu'il n'existe aucune alternative thérapeutique et dans le cas de médicaments destinés au traitement de maladies potentiellement mortelles, les législateurs sont généralement prêts à accepter un niveau plus élevé d'incertitude dans l'évaluation du rapport bénéfice/risque. Ainsi que discuté dans cet article, ce changement de paradigme devrait également être mis en œuvre afin de permettre un accès réel aux médicaments contre la TB en cours d'évaluation clinique. Au-delà, sont analysés dans cet article les défis liés à la mise en place d'un régime d'accès sûr et efficace aux médicaments expérimentaux dans le contexte de la MDR/RR-TB ainsi que les principes éthiques et les arguments des droits humains en faveur de l'élaboration de tels programmes.

RESUMEN

En la edición revisada de las orientaciones éticas para la ejecución de la Estrategia Fin a la Tuberculosis se ha agregado un nuevo capítulo sobre el uso compasivo y el acceso ampliado a los fármacos antituberculosos. Los programas de uso compasivo y acceso ampliado autorizan el acceso, fuera del contexto de los ensayos clínicos, a los fármacos que aún no han recibido autorización para la comercialización. Estas medidas tienen por objeto autorizar el acceso de los pacientes con tuberculosis (TB) multirresistente (MDR) o resistente a rifampicina (RR) a los fármacos en curso de investigación sin que exista una plena evidencia de su eficacia y seguridad, cuando ninguna otra opción terapéutica está disponible. Al incluir este tema, las pautas reconocen la necesidad urgente de ofrecer a estos pacientes todos los tratamientos posibles, en cumplimiento de consideraciones de justicia, derechos humanos, dignidad humana, autonomía de la persona y protección de la comunidad. Los entes reguladores suelen aceptar un nivel más alto de incertidumbre en el análisis de los riesgos y los beneficios de los fármacos destinados a enfermedades potencialmente mortales, cuando existe una necesidad médica insatisfecha y reconocen así un cambio de paradigma que, como se propone en el artículo, también se debería aplicar para lograr un acceso efectivo a los fármacos antituberculosos experimentales. Además, los autores analizan las dificultades relacionadas con la elaboración de un método seguro y efectivo de acceso a los fármacos experimentales en el contexto de la MDR/RR-TB y también consideran los principios éticos y los argumentos de derechos humanos en favor de la creación de este tipo de programas.