BMC Global and Public Health

CORRESPONDENCE

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Recommendations for the optimal introduction of novel antibiotics to treat uncomplicated gonorrhoea in the face of increasing antimicrobial resistance: a case study with zoliflodacin

Fernando Pascual[1*], Carmen Au[1], Chido Dziva Chikwari[2,3], Pierre Daram[1], Carolyn Deal[4], Angelica Espinosa Miranda[5], Yonatan H. Grad[6], Edward WIII Hook[7], Rossaphorn Kittiyaowamarn[8], Alison Luckey[1], Nicola Low[9], Venessa Maseko[10], Remco P. H. Peters[11,12,13], Teri Roberts[1], Magnus Unemo[14,15] and Subasree Srinivasan[1]

Abstract

New, first-in-class oral antibiotics like zoliflodacin, developed in a public–private partnership, require an optimal introduction strategy while ensuring antibiotic stewardship. Zoliflodacin, given as a single dose for uncomplicated urogenital gonorrhoea, recently demonstrated non-inferiority to ceftriaxone plus azithromycin and safety in a phase 3 randomised controlled trial. Following regulatory approval, zoliflodacin could improve sexually transmitted infection (STI) management and help address the threat of untreatable gonorrhoea, as levels of resistance to current first-line treatments increase. The Global Antibiotic Research & Development Partnership (GARDP) convened an expert meeting during the 2023 STI and HIV World Congress to discuss key questions about the introduction of zoliflodacin in low- and middle-income countries (LMICs). The questions included: which patients to treat in which situations, the timing of introduction, and what additional evidence is needed to change policy for the use of new antibiotics for gonorrhoea. Recommendations from the expert group included: the generation of evidence for the role of a drug like zoliflodacin in clinical treatment failures; the need for additional antimicrobial resistance surveillance; investigation of the role of novel diagnostic approaches, such as point-of-care tests, to improve stewardship; study of preferences and values among the population in need; and modelling of the emergence of *N. gonorrhoeae* resistance and transmission in different scenarios. Forthcoming World Health Organization (WHO) global guidelines could outline recommendations for a new oral antibiotic like zoliflodacin based on existing evidence, and rational approaches for certain populations or use cases, while the evidence base is further strengthened.

Keywords Public health, Sexually transmitted infections, Antimicrobial resistance, *Neisseria gonorrhoeae*, Gonorrhoea, Health policy, Treatment guidelines

*Correspondence:
Fernando Pascual
fpascual@gardp.org
Full list of author information is available at the end of the article

Background

There were an estimated 82.4 million [47.7 million–130.4 million] new cases of gonorrhoea in 2020, the majority in low- and middle-income countries (LMICs) [1, 2]. In most countries, effective management and control of gonorrhoea are hindered by a lack of comprehensive population-level epidemiological and antimicrobial resistance (AMR) surveillance data about increasing levels of *Neisseria gonorrhoeae* resistance [3]. In 2018, among countries participating in the World Health Organization (WHO) global Gonococcal Antimicrobial Surveillance Programme (GASP), 6/68 (9%) and 44/61 (72%) reported that ≥ 5% of isolates tested had resistance/decreased susceptibility to ceftriaxone and resistance to azithromycin, respectively [4]. This is the last remaining combination regimen for empiric treatment, which highlights the threat of untreatable gonorrhoea and the need for both rational use of existing treatments and the development of new antibiotics [5]. Complications of untreated gonorrhoea can include pelvic inflammatory disease, ectopic pregnancy, infertility, penile oedema, epididymitis and disseminated gonococcal infection. Moreover, sexually transmitted infections (STIs) may increase the risk of HIV acquisition, so strengthened screening and treatment is necessary to achieve program targets for both [6].

Zoliflodacin is a first-in-class spiropyrimidinetrione, which was developed by the Global Antibiotic Research and Development Partnership (GARDP) as a single-dose oral treatment for uncomplicated gonorrhoea [7, 8]. In a phase 3 randomised controlled trial, zoliflodacin was non-inferior to the combination of ceftriaxone and azithromycin [9], the current WHO-recommended treatment for gonorrhoea [10]. Zoliflodacin has in vitro activity against strains resistant to penicillin, cefixime, ceftriaxone, azithromycin, tetracycline, and fluoroquinolones [11]. The propensity for the emergence of resistance to zoliflodacin appears to be low. Although zoliflodacin-resistant mutants containing GyrB S467N and/or D429N substitutions have been selected in a hollow fibre infection model (HFIM) [12], no resistance to zoliflodacin has been identified in contemporary clinical isolates tested to date [13]. To allow routine zoliflodacin susceptibility testing in the future, work to establish minimum inhibitory concentration (MIC) breakpoints and disk and gradient diffusion methods are in progress. Molecular tests for relevant GyrB mutations would allow their detection in clinical settings.

GARDP held a workshop with experts from academic institutions, national public health agencies from South Africa and Thailand and international organizations, including WHO, at the STI and HIV World Congress in Chicago on July 26, 2023. The members of the group were, in alphabetical order: Carmen Au, Laura Bachmann, Benjamin Blumel, Chido Dziva Chikwari, Pierre Daram, Carolyn Deal, Angélica Espinosa, Cecilia Ferreyra, Pamela Gaspar, Yonatan H. Grad, Edward W III Hook, Chris Kenyon, Rossaphorn Kittiyaowamarn, Jeff Klausner, David Lewis, Nicole Lima, Nicola Low, Alison Luckey, Albert Manasyan, Venessa Maseko, Leandro A. Mena, John Mueller, Lori Newman, Fernando Pascual, Remco P.H. Peters, Teri Roberts, Subasree Srinivasan and Magnus Unemo. The group described the local barriers to programmatic adoption and opportunities to optimise effective STI management and introduction strategies for future new antibiotics, like zoliflodacin. Table 1 shows the key questions which emerged from discussions about the introduction and optimal use of new treatments, like zoliflodacin, in LMICs, particularly where there is a high prevalence of drug-resistant gonorrhoea.

Table 1 Key themes and questions for implementation of new antibiotics, like zoliflodacin

Context/local environment	- What are the main barriers to programmatic adoption of new treatments locally (e.g. in Thailand and South Africa)? - How do countries identify patients in need? - What is/are the use case(s) for the new treatment? For example: o Limited to second-line treatment (e.g. for clinical or microbiological treatment failures)? o Used for first line where proportion of isolates of ceftriaxone-resistant gonococci is high (e.g. ≥ 5%)? o Used only for treating people from high-risk groups and their partners?
Guideline/policy	- When is it best to introduce a new treatment?
	- Do treatment combinations need to be investigated and, if so, which ones?
	- Which populations would benefit most from the introduction of a new treatment (i.e. partners of those receiving second-line treatment, high-risk groups)?
	- What additional data is needed to support decision-making for inclusion into guidelines?
	- What is a suitable threshold of AMR to justify a change in first-line treatment?
Sustainability	- How can the adoption of a new treatment be scaled up (while ensuring equitable access)? - Is the new treatment cost-effective?

Context/local environment issues

The main barriers to programmatic implementation exposed by both Thai and South African representatives were how to ensure the appropriate use of antibiotics and delay the development of AMR. The absence of affordable, rapid diagnostic point-of-care tests (POCTs) for pathogen identification impedes the transition from syndromic to aetiological management. For *N. gonorrhoeae*, the use of tests that do not detect molecular markers of AMR challenges the rational use of both existing and new antibiotics. Currently, diagnostic tests that allow rapid identification of *N. gonorrhoeae* are either unavailable in LMICs or are not true POCTs, meaning that testing and treatment in the same consultation are not possible. Numerous POCTs are under development, but it typically takes several years before new tests are broadly adopted and most have an unclear future in LMICs, e.g. due to their high cost. Attendees supported the use of POCTs, noting that individuals with symptomatic STIs often present at primary care facilities where there are no laboratories, as well as the challenges accessing secondary-level facilities following a clinical treatment failure referral. The development of affordable POCTs that are accessible in countries is thus considered a priority [14].

Country representatives from Thailand and South Africa also stressed the need to strengthen surveillance to support the current syndromic management approach to identify specific population groups in need where diagnostic tests remain unavailable. Participants from Thailand also discussed challenges to identifying and treating partners and proposed exploring expedited partner therapy as it outperforms other partner treatment management approaches [15].

Experts discussed different scenarios for the deployment of new treatments like zoliflodacin, including a stepwise strategy that would initially reserve an antibiotic like zoliflodacin for treatment failures before later expanding to first-line. Experts agreed that decisions about the introduction strategy would require data and modelling on whether there is an appropriate prevalence threshold of resistance to current treatments that would necessitate a switch in first-line treatment, something which is not yet empirically established. The threshold of 5% of all isolates tested in a country recommended by WHO for gonorrhoea [16] could serve as a starting point but needs further evaluation. Looking at historical data on discontinued antibiotics due to a guideline change was suggested to provide insights. Regardless, detection of treatment failures is considered to remain a challenge.

Experts suggested that an antibiotic like zoliflodacin could be introduced and used as the initial treatment in specific circumstances, like in regions with a higher prevalence of ceftriaxone-resistant gonococci, but only when accompanied by current AMR surveillance data to confirm the pattern of resistance, and availability of zoliflodacin susceptibility testing (using recommended MIC breakpoints, once available).

Guidelines/policy issues

To support policy change, the group recommended the use of modelling of various resistance-minimising strategies [17]. Specified outputs from modelling studies included (i) the predicted time to emergence and rate of transmission of resistance to the new drug, using different introduction strategies; (ii) outcomes to be monitored following introduction in different population groups; and (iii) the advantages and disadvantages of using an antibiotic like zoliflodacin as part of combination therapy, considering pharmacokinetics and pharmacodynamics, treatment synergy/antagonism and potential for drug-drug interactions. Experts agreed that country- or region-specific modelling would be needed. Different models would require: data obtained from settings with high treatment failure or resistance rates for ceftriaxone; behavioural characteristics (e.g. sexual mixing); prevalence (including in asymptomatic individuals and the impact that treating this group would have on population transmission); effect of the new drug on non-gonococcal *Neisseria* species; number of misdiagnosed treatment failures; and type and extent of AMR (e.g. time to resistance of available over the counter vs. prescription antibiotics), among others.

The group of experts proposed that mathematical models of gonorrhoea transmission would be needed to estimate how the change in one specific parameter impacts outcomes, such as different treatment approaches (e.g. syndromic versus aetiological management) and how this impacts the use of antibiotics. The rate of zoliflodacin resistance development over time could be modelled using a within-host model informed by HFIM data. Modelling efforts may, however, be challenging. A lack of quality input data requires substitution with important assumptions, and different data needs and treatment approaches may be warranted in different contexts. Nevertheless, it was thought that models based on general characteristics should still be possible. It was noted that modelling could also inform the discussion on an appropriate AMR threshold to switch first-line recommendations in guidelines.

The group also addressed the need for additional data to support policy change. Experts discussed that studying the efficacy of a new drug like zoliflodacin compared to alternative treatment options for ceftriaxone-resistant strains could be important in the future, including treatment follow-up to determine clinical and microbiological outcomes (test of cure) and the possible need for (re-)

testing and re-treatment, which will require robust monitoring and evaluation systems.

Sustainability issues

Although sustainability was not discussed at length, the need for a public health approach that is rooted in equity was highlighted. Evidence on the health benefits, economic values and preferences, and values in the general and in high-risk populations is needed. In addition, understanding the implementation of guidelines and the patient pathway in countries will help inform the introduction of new products such as zoliflodacin. Real-world evidence and observational studies, which are planned to address this, should be done in partnership with WHO and countries to help ensure programmatic relevance and sustainable use. Cost-effectiveness studies could also be needed to inform introduction in countries.

Conclusions

The workshop provided valuable expert and regional insights and recommendations on suggested pathways for the immediate introduction and use of a new antibiotic, helped identify knowledge gaps, and informed specific research work needed to generate evidence in support of decision-making for inclusion in future guideline updates, following the potential registration of a new antibiotic. For instance, recommendations included the generation of evidence for the role of a new drug for treatment failures; additional AMR studies to support surveillance; investigation of novel diagnostic approaches (e.g. identification and resistance POCTs to improve stewardship); better understanding of preferences and values among the population in need; and modelling the emergence of *N. gonorrhoeae* resistance and transmission under different conditions. Research needs to be population- and region-specific to inform whether to introduce a new antibiotic immediately to provide an oral option that will help reduce the selective pressure on the rate of development of ceftriaxone resistance, or to limit the introduction of the new antibiotic until diagnostic and surveillance capacity increases; and to determine the best options for stewardship within an equitable public health approach. Forthcoming guidelines could outline recommendations for a new antibiotic like zoliflodacin based on the phase 3 clinical controlled study outcome, existing evidence, and rational approaches for certain populations or use cases, while further strengthening the evidence base in parallel. Further discussions are needed on the expanded use of zoliflodacin as the first line and on what additional research is needed to support this transition.

Abbreviations

AMR	Antimicrobial resistance
GARDP	Global Antibiotic Research & Development Partnership
HIV	Human immunodeficiency virus
GASP	Gonococcal Antimicrobial Surveillance Programme
HFIM	Hollow fiber infection model
LMIC	Low- and middle-income country
NG	*Neisseria gonorrhoeae*POCT: point-of-care tests
STI	Sexually transmitted infections
WHO	World Health Organization

Acknowledgements

Expert group that participated in the workshop convened during the STI and HIV World Congress in Chicago in July 2023 (Chicago workshop expert group). Members of the group: Carmen Au, Laura Bachmann, Benjamin Blumel, Chido Dziva Chikwari, Pierre Daram, Carolyn Deal, Angélica Espinosa, Cecilia Ferreyra, Pamela Gaspar, Yonatan H. Grad, Edward W III Hook, Chris Kenyon, Rossaphorn Kittiyaowamarn, Jeff Klausner, David Lewis, Nicole Lima, Nicola Low, Alison Luckey, Albert Manasyan, Venessa Maseko, Leandro A. Mena, John Mueller, Lori Newman, Fernando Pascual, Remco P.H. Peters, Teri Roberts, Subasree Srinivasan and Magnus Unemo.

Authors' contributions

All the authors attended the workshop and participated in discussions during the workshop except TR. TR and FP wrote the manuscript and all authors reviewed and approved. All authors read and approved the final manuscript.

Funding

This workshop was funded by the governments of the United Kingdom (GAMRIF, part of DHSC), Germany (BMBF), the Netherlands (DGIS and VWS), as well as the European Union (EC DG HERA). The views expressed in this publication are those of the authors and not necessarily those of the funding bodies.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

Zoliflodacin is co-developed by the Global Antibiotic Research & Development Partnership (GARDP) in collaboration with Innoviva Specialty Therapeutics, a subsidiary of Innoviva, Inc. (Nasdaq: INVA). CA, AL, PD, SS, TR and FP are employees of GARDP. GARDP covered the expenses for RK. CD, HE, RK and MU have participated in zoliflodacin development. The remaining authors declare that they have no competing interests.

Author details

[1]Global Antibiotic Research & Development Partnership, Geneva, Switzerland. [2]Medical Research Council (MRC) International Statistics & Epidemiology Group, Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK. [3]The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe. [4]National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD, USA. [5]Ministerio da Saude, Departamento de HIV/AidsTuberculose, Hepatites Virais E Infecoes Sexualmente Transmissíaveis, Brasília, Distrito Federal, Brasil. [6]Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [7]The University of Alabama at Birmingham, Birmingham, AL, USA. [8]Bangrak Sexually Transmitted Infections (STIs) Center, Division of AIDS and STIs, Department of Disease Control, Ministry of Public Health, Bangkok, Thailand. [9]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [10]Centre for HIV and Sexually Transmitted Infections (STIs), National Institute for Communicable Diseases, National Health Laboratory Service, Johannesburg, South Africa. [11]Foundation for Professional Development, Research Unit,

East London, South Africa. [12]Department of Medical Microbiology, University of Pretoria, Pretoria, South Africa. [13]Division of Medical Microbiology, University of Cape Town, Cape Town, South Africa. [14]WHO Collaborating Centre for Gonorrhoea and Other STIs, Orebro University, Orebro, Sweden. [15]Institute for Global Health, University College London, London, UK.

Received: 16 April 2024 Accepted: 25 July 2024
Published online: 03 September 2024

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