

medicines
patent
pool



**PRIORITISATION OF
HIV, HEPATITIS C
AND TUBERCULOSIS
MEDICINES
FOR IN-LICENSING
BY THE
MEDICINES PATENT
POOL - 2020**

TABLE OF CONTENTS

1.	Introduction	4
2.	Priorities in HIV	5
3.	Priorities in Hepatitis C	8
4.	Priorities in Tuberculosis	8
5.	Long-Acting Formulations in HIV, HCV, TB and Malaria	13

AKNOWLEDGEMENTS

The Medicines Patent Pool (MPP) is grateful to the experts participating in various meetings including the Unitaid Global Technical Consultation Meeting on Long Acting Technologies to Prevent and Treat Major Infectious Diseases, 10th IAS Conference on HIV Science, the Paediatric Antiretroviral Drug Optimization (PADO), and the presentations made available on-line from the Conference on Retroviruses and Opportunistic Infections (CROI) whose insights contributed to the updating of the MPP prioritisation document. Discussions over the past year with the World Health Organization (WHO), Unitaid and a range of experts in academic, medical, public health and community-based organisations were also helpful to further understand the potential of different medicines. The final assessment, however, is the responsibility of MPP alone.

1. INTRODUCTION

MPP's work on licensing medicines to facilitate affordable access in low- and middle-income countries (LMICs) starts with the identification of target medicines that could have a significant role in improving public health outcomes in LMICs and where MPP licensing could contribute to broader access. In order to do this, MPP has developed a prioritisation framework which it has regularly applied since 2011 to identify target medicines for licensing. Initially focusing on HIV alone, the prioritisation framework was subsequently adapted to hepatitis C and tuberculosis. Over time, additional criteria were added to ensure the framework took properly into account a range of different clinical, intellectual property, licensing and market criteria. More recently, a separate framework was developed for identifying possible target medicines for in-licensing in other therapeutic areas¹. The present document, however, focuses on HIV, hepatitis C and tuberculosis and includes a new section on long-acting formulations that are relevant to these three diseases plus malaria.

The framework for this year's assessment remained unchanged from last year. It takes into account recent data on candidate medicines, as well as an early assessment of their potential for use in LMICs. It also considers whether they are patent-protected in LMICs, whether any access strategies (e.g. licensing) are already in place and how the market is likely to evolve making MPP's licensing approach suitable (or not) for facilitating uptake in LMICs.

In addition to identifying MPP priorities for in-licensing, we continue to also identify promising new medicines in early clinical development that may represent future game-changers. These are currently being placed in a watch list, as further data from clinical trials would be required for a full assessment. We also look at approved medicines that may not be immediate priorities, but may provide interesting opportunities to consider for future treatment.

For the first time this year, we have also begun to look at broadly neutralising antibodies (bNAbs) that could be used for the treatment or prevention of HIV. While it is too soon to have clarity on whether and, if so when, bNAbs are likely to play an important role in LMICs, a number of ongoing clinical trials will provide useful information that will contribute to better understanding their potential. In the meantime, MPP has begun its own assessment on whether the MPP model could be applied to the field of biotherapeutic products, phase one of which will be completed later this year.

¹ A description of the framework currently used by MPP to prioritise essential medicines in other therapeutic areas is available [HERE](#)

2. PRIORITIES IN HIV

TABLE 1 – SUMMARY OF PRIORITY ARVs FOR MPP

ARV	CLASS	MPP ANALYSIS
Cabotegravir long-acting injectable	Integrase inhibitor	<p>CAB-LA is being clinically investigated for PrEP and is currently in Phase III studies.^{2 3} Results from Phase II studies^{4 5} showed high levels of acceptability and efficacy for the bimonthly regimen with mild and moderate injection site reactions. CAB-LA for PrEP does not require a cold chain and seems like a potentially important option for PrEP in LMICs. The long pharmacokinetic tail of CAB-LA, however, raises concerns about emergence of drug resistance, and further understanding of this will be important.⁶ It will also be important to better understand how the market for PrEP in LMICs could evolve and the likely costs of developing and manufacturing generic CAB-LA.</p> <p>CAB-LA has also been investigated for HIV treatment. Phase III clinical trials proved the potential of CAB-LA together with rilpivirine LA for HIV maintenance therapy in virally suppressed individuals. While the application for marketing approval was rejected by the USFDA in December 2019, due to issues relating to Chemistry Manufacturing and Controls (CMC),^{7 8} there were no safety or efficacy concerns and recent data from CROI2020 proved the effectiveness and tolerability of bimonthly dosing.⁹ A new Phase I/II study for virally suppressed children and adolescents has also been initiated with results expected in April 2021.¹⁰ The cold chain requirement of RPV-LAI, however, makes this regimen challenging to be implemented in resource-limited settings.</p> <p>CAB-LA is now also being explored in dual combination with VRC07-523LS, a broadly neutralising monoclonal antibody, in Phase II studies¹¹ for virally suppressed PLHIVs.</p> <p>The main patent on cabotegravir has been filed or granted in many LMICs and expires in 2026. In addition, a patent on the long-acting parenteral formulation expires in 2031.¹² The drug has not been licensed for generic production.</p> <p>While cabotegravir is in the Priorities List, primarily for the PrEP indication (in view of the cold chain requirements for the companion drug for its use in treatment) further consultations are likely required to further understand the potential for facilitating access to the product by licensing to generic manufacturers.</p>

MPP has also developed a watchlist of promising drug candidates that are in earlier stages of development, outlined in Table 2. While early data suggests that these ARVs have strong potential in LMICs, there is insufficient clinical data at this stage to enable full prioritisation. MPP, however, would already begin engagement with the developers to explore possible future scenarios, given the high likelihood of them being prioritised in future.

² <https://clinicaltrials.gov/ct2/show/NCT02720094>

³ <https://clinicaltrials.gov/ct2/show/NCT03164564>

⁴ <https://clinicaltrials.gov/ct2/show/NCT02076178>

⁵ <https://clinicaltrials.gov/ct2/show/NCT02178800>

⁶ <https://www.nature.com/articles/s41467-019-10047-w>

⁷ <https://viivhealthcare.com/en-gb/media/press-releases/2019/april/viiv-healthcare-submits-new-drug-application-to-us-fda-for-the-first-monthly-injectable-two-drug-regimen-of-cabotegravir-and-rilpivirine-for-treatment-of-hiv/>

⁸ <https://viivhealthcare.com/en-gb/media/press-releases/2019/december/complete-response-letter-from-us-fda/>

⁹ <https://viivhealthcare.com/en-us/us-news/us-articles/2020/viiv-healthcare-presents-positive--48-week-data-from-phase-iii-s/>

¹⁰ <https://clinicaltrials.gov/ct2/show/study/NCT03497676>

¹¹ <https://clinicaltrials.gov/ct2/show/NCT03739996>

¹² MPP-UNITAID (2018), Intellectual Property Report on Long-Acting Technologies

TABLE 2 – SUMMARY OF PROMISING ARVs IN EARLY DEVELOPMENT (MPP WATCHLIST)

ARV	CLASS	MPP ANALYSIS
Islatravir (MK-8591) Phase I, II, III and pre-clinical (depending on formulation and indication)	Nucleoside reverse transcriptase translocation inhibitor (NRTTI)	<p>Islatravir is a nucleoside reverse transcriptase translocation inhibitor (NRTTI), a new class of ARVs, and is currently being developed for the prevention and treatment of HIV.¹³ It is a promising molecule with long-acting properties and, pending further data from efficacy trials, is considered likely to play an important role in the prevention and/or treatment of HIV in the future.</p> <p>Results from a Phase I study¹⁴ showed that single doses of islatravir as low as 0.5 mg were highly efficacious in treatment-naïve patients with no detection of viral resistance. A phase 2b study¹⁵ demonstrated that ISL+DOR combination could be a potential once-daily two-drug regimen with minimal impact on bone mineral density and similar changes in fat distribution, weight, and BMI as compared to the triple regimen that also included lamivudine (3TC).¹⁶ Although no serious drug-related adverse events (AE) were reported, these studies excluded pregnant, breastfeeding women and patients with hepatitis B or C. Phase III clinical studies are now in progress to evaluate a once-daily fixed dose combination of ISL/DOR (0.75/00 mg) for treatment-naïve, virally suppressed and heavily treatment-experienced (HTE) patients.^{17 18 19 20}</p> <p>Islatravir is also being studied as a long-acting subdermal implant (Phase I)²¹ and in oral doses for PrEP.²² A recent update from CROI also supported the possibility of ISL as a simplified post-exposure prophylaxis (PEP) agent.²³</p> <p>While the patent on islatravir has not been filed in LMICs (except Mexico), there are patents pending in a large number of LMICs on the use of islatravir for the treatment or prophylaxis of HIV with a dosing less frequent than once a day, expiring in 2037. There are also various patent applications on islatravir implant and on the use of islatravir in combination with other ARVs.</p>

¹³ <https://www.merck.com/pipeline/index.html>

¹⁴ <https://clinicaltrials.gov/ct2/show/NCT02217904>

¹⁵ <https://clinicaltrials.gov/ct2/show/NCT03272347>

¹⁶ <http://www.croiconference.org/sessions/islatravir-metabolic-outcomes-phase-iiib-trial-treatment-naive-adults-hiv-1>

¹⁷ <https://clinicaltrials.gov/ct2/show/NCT04223778>

¹⁸ <https://clinicaltrials.gov/ct2/show/NCT04223791>

¹⁹ <https://clinicaltrials.gov/ct2/show/NCT04233216>

²⁰ <https://clinicaltrials.gov/ct2/show/NCT04233879>

²¹ <https://www.mrknnewsroom.com/news-release/research-and-development-news/merck-presents-early-evidence-extended-delivery-investiga>

²² <https://clinicaltrials.gov/ct2/show/NCT04003103>

²³ <http://www.croiconference.org/sessions/weekly-oral-islatravir-provides-effective-pep-against-iv-challenge-sivmac251>

<p>Lenacapavir (GS-6207; GS-CA2)</p> <p>First-in-class</p> <p>Phase II</p>	<p>Capsid inhibitor</p>	<p>Lenacapavir (or GS-6207) is another promising new molecule with long-acting properties that could make a significant contribution to HIV treatment in the future.</p> <p>Capsid inhibitors are a new class of drugs that function by interfering with the assembly and disassembly of the viral capsids. The drug binds to conserved sites on the capsids, rendering it effective against multiple HIV strains. Additionally, the drug is able to block viral genetic material from entering the host nucleus.</p> <p>Lenacapavir is now being investigated for both treatment-naïve and treatment-resistant PLHIVs. Recent Phase I data on the potency, safety and in vitro resistance of lenacapavir as a subcutaneous injection demonstrate its utility as a potential long-acting HIV therapy candidate, with a dosing interval of up to every six months in a broad range of PLHIVs regardless of their treatment history. The most common adverse events were mild & moderate injection site pains.²⁴</p> <p>Based on these results, two new clinical trials have been initiated to further study lenacapavir in combination with TAF/FTC & BIC for treatment-naïve patients²⁵ and heavily treatment-experienced patients with multidrug resistant HIV-1.²⁶ Latest updates from CROI2020 indicate that, in addition to the sub-cutaneous LAI formulation, lenacapavir oral tablets were also generally well tolerated with no serious adverse events.</p> <p>Patents on lenacapavir have been granted or filed in a large number of LMICs, and are expected to expire in 2034-37.</p>
<p>GSK3640254</p> <p>Phase II</p>	<p>Maturation inhibitor</p>	<p>GSK3640254 (or GSK '254) is a new maturation inhibitor currently in phase 2, which inhibits HIV replication by working in the late stage of the viral lifecycle thus producing immature, noninfectious virus.²⁷ Maturation inhibitors are not cross-resistant to other classes of HIV drugs and could be an important new class for HIV treatment.</p> <p>GSK '254 is being studied as a capsule in 1 milligram (mg), 10 mg and 100 mg dosing strengths. Results from Phase I studies^{28 29} in adult healthy volunteers have shown that the drug is safe, tolerable and has good bioavailability for its two salt forms (mesylate and hydrochloride). These two studies supported further development as a once-daily oral pill. Phase II clinical trials³⁰ have started in HIV-1 infected treatment naïve patients.</p> <p>Based on information available to date, patents on GSK '254 likely expire around 2032.</p>

MPP will also continue to monitor the following approved products. This means that while these products have interesting characteristics that may turn them into promising candidates for licensing, several questions remain on how these products could be utilised in public health settings to meet the treatment and/or prevention needs in developing countries. They are therefore not considered at present a priority for MPP.

²⁴ <https://www.gilead.com/news-and-press/press-room/press-releases/2019/11/gilead-presents-data-on-investigational-hiv-1-capsid-inhibitor-gs-6207-as-a-potential-component-of-long-acting-hiv-therapy>

²⁵ <https://clinicaltrials.gov/ct2/show/NCT04143594>

²⁶ <https://clinicaltrials.gov/ct2/show/NCT04150068>

²⁷ http://www.natap.org/2019/Pharm/Pharm_01.htm

²⁸ <https://clinicaltrials.gov/ct2/show/NCT03231943>

²⁹ <https://clinicaltrials.gov/ct2/show/NCT03575962>

³⁰ <https://clinicaltrials.gov/ct2/show/NCT03784079>

TABLE 3 – SUMMARY OF APPROVED ARVS TO BE FURTHER MONITORED (MPP MONITORING LIST)

ARV	CLASS	MPP ANALYSIS
Doravirine (DOR) <i>Approved by the FDA in Aug 2018</i>	Non-nucleoside reverse-transcriptase inhibitor (NNRTI)	<p>Doravirine (DOR) was approved in August 2018 as a standalone agent as well as in combination with tenofovir disoproxil fumarate and lamivudine. It is a new-generation NNRTI anticipated to be effective against a broad panel of NNRTI-resistant viruses. At a daily dose of 100mg, DOR has been shown to be as effective as efavirenz or boosted darunavir as part of initial therapy, with improved safety and tolerability.³¹ Doravirine is also being clinically investigated in combination with islatravir as a once-daily FDC for treatment-naïve, virally suppressed and heavily treatment-experienced (HTE) patients.</p> <p>Doravirine has a more favorable lipid profile compared with other NNRTIs and can likely be used for patients with known resistance to other drugs in the class.³² Phase I PK study of doravirine is currently in progress for paediatric and adolescent patients, with results expected in March 2021.³³</p> <p>Importantly, DOR & DOR/3TC/TDF are contraindicated for antimycobacterials rifampicin and rifapentine, which would be challenging in LMICs with high levels of TB/HIV co-infection. Significant decreases in doravirine plasma concentrations may occur, which may decrease the effectiveness of DOR & DOR/3TC/TDF.³⁴ Doravirine has not been studied in pregnant women.</p> <p>Patents on DOR are expected to expire in 2031 and have not been licensed for generic production.</p> <p>Placing of doravirine in the “Monitoring” list is pending further consultation with WHO and other experts. Some experts consulted indicated that doravirine could play an important role in first-line treatment for people with tolerability problems to WHO’s current preferred first-line. Further consultations are required.</p>
Rilpivirine (RPV)-LA Phase III	NNRTI	<p>Rilpivirine long-acting injectable (RPV-LA) in combination with CAB-LA was submitted for approval by the USFDA for treatment maintenance in adults.³⁵ It is also currently in Phase II investigations for virally suppressed children & adolescents.³⁶</p> <p>While the combination of CAB-LA and RPV-LA could be options for long-term treatment simplification, the cold chain requirement of the current formulation of RPV-LA makes this regimen less suitable for use in resource-limited settings. MPP will continue to monitor the progress with RPV-LA formulations, but does not consider it a priority at present.</p> <p>Patents on rilpivirine expire in 2022/25 and on the injectable formulation in 2026/27. Licences have been granted to several generic manufacturers for the oral formulation, but generic products are not yet on the market.</p>

Since last year, it has been decided to drop one of the medicines that was previously in the “Monitoring” list, namely fostemsavir (FTR). FTR was approved by the USFDA in July 2020 and was developed for the treatment of highly treatment experienced adults, which would cater to a very small population of HIV-1 infected patients in resource-limited settings. The high cost of raw materials for API manufacturing, along with the small market would likely be a deterrent for the generic production of FTR. It is therefore not being considered as a candidate for licensing by MPP.

BROADLY NEUTRALISING ANTIBODIES (BNABS) & BIOLOGICS

Continuous exposure to HIV over the last 3 decades has caused a small number of PLHIVs to develop highly potent and reactive antibodies – now referred to as broadly neutralising antibodies (bNAbs).³⁷ More

³¹ Squires, KE, Molina, J and Sax, P et al (2017) Fixed-dose combination of DOR/3TC/TDF is non-inferior to EFV/F/TDF in treatment-naïve adults with HIV-1 infection: week 48 results of phase 3 DRIVE-AHEAD study, presented at IAS 2017

³² <https://blogs.jwatch.org/hiv-id-observations/index.php/doravirine-sets-new-standard-nnrtis-role-hiv-treatment-today/2018/09/09/>

³³ <https://clinicaltrials.gov/ct2/show/NCT03332095>

³⁴ <https://www.mrknewsroom.com/news-release/research-and-development-news/merck-announces-presentation-phase-2b-results-investigati>

³⁵ <https://clinicaltrials.gov/ct2/show/NCT02951052>

³⁶ <https://clinicaltrials.gov/ct2/show/NCT03497676>

³⁷ Dashti et al (Mar 2019), Trends in Molecular Medicine, 25 (3), 228-240 <https://doi.org/10.1016/j.molmed.2019.01.007>

than 200 different bNAb have been isolated to date, which vary in their coverage of global HIV isolates as well as in their potency, or the amount required to neutralise the virus.³⁸ One of the limitations of individual bNAbs has been the emergence of antibody resistance due to the high diversity and mutation rate of HIV-1 and hence the current strategies include development of combination bNAbs with improved potency, longer half-life and broader coverage for the treatment and prevention of HIV.³⁹

The target for bNAbs currently being investigated in humans include the CD4 binding site, the V3- and V1/V2-glycan sites and gp41-gp120 interface on the HIV virus.⁴⁰

As MPP is currently undertaking an assessment on whether, and if so how, to apply its model to facilitate affordable access to biologics in LMICs, it is not undertaking a full assessment of bNAbs to identify priorities for licensing at this stage. However, it is monitoring their development and use and will consider prioritising them, depending on the results of the ongoing assessment.

TABLE 4 – BROADLY NEUTRALISING ANTIBODIES APPROVED OR IN LATE-STAGE DEVELOPMENT

ARV	CLASS	MPP ANALYSIS
Ibalizumab <i>Approved by the FDA in Mar 2018</i>	CD4 binding	<p>Ibalizumab (IBA) was approved by USFDA for heavily treatment-experienced patients with MDR HIV-1 infection failing their current ARV regimen. It is intended for use in combination with other HIV drugs.⁴¹ Ibalizumab binds to the CD4 receptor, thus blocking entry of HIV-1 virus into CD4 cells. As per the results from Phase 3 studies, Ibalizumab had significant antiviral activity during a 25-week study, wherein 43% of participants reached a viral load <50 copies/mL and 50% <200 copies/mL.⁴² Ibalizumab is administered intravenously at a dose of 800 mg every 2 weeks following a single intravenous loading dose of 2000 mg.</p> <p>Recent update from CROI2020 showed that significant viral efficacy for highly treatment experienced patients was achieved with IBA in combination with one or two active ARV drugs (FTR, DTG, TDF, RPV were used). IBA+DTG combination was most effective.⁴³</p>
Leronlimab (PRO 140) <i>Phase III</i>	CCR5	<p>Leronlimab is a viral-entry inhibitor with the CCR5 receptor as its binding site. It is currently being investigated as a weekly subcutaneous injection (Phase 2/3) in combination with existing ART regimen for treatment-experienced patients (700 mg dose)⁴⁴ and as monotherapy for virally suppressed patients (without ART regimen).⁴⁵ As per the early results presented at CROI 2019, 65% virological failure rate was observed for the 350 mg arm monotherapy study⁴⁶, but the innovator indicated in August 2019 better viral suppression rates after 10 weeks – 68% (250 mg), 94% (525 mg) and 85% (700 mg).⁴⁷ Final results are expected in July 2020.</p> <p>In addition to HIV, leronlimab is also being tested for breast cancer and very recently, has shown promising early results for treatment of COVID-19.^{48 49}</p>

³⁸ Burton et al (May 2016), Annual Review of Immunology, 34:635-659 <https://doi.org/10.1146/annurev-immunol-041015-055515>

³⁹ Gruell et al (Nov 2018), Retrovirology, 15:73 <https://doi.org/10.1186/s12977-018-0455-9>

⁴⁰ Dashti et al (Mar 2019), Trends in Molecular Medicine, 25 (3), 228-240 <https://doi.org/10.1016/j.molmed.2019.01.007>

⁴¹ https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/761065Orig1s000ltr.pdf

⁴² <https://clinicaltrials.gov/ct2/show/study/NCT02475629>

⁴³ <http://www.croiconference.org/sessions/comparable-efficacy-ibalizumab-combination-1-or-2-fully-active-agents>

⁴⁴ <https://clinicaltrials.gov/ct2/show/NCT03902522>

⁴⁵ <https://clinicaltrials.gov/ct2/show/NCT02859961>

⁴⁶ <http://www.croiconference.org/sessions/pro-140-sc-long-acting-single-agent-maintenance-therapy-hiv-1-infection>

⁴⁷ <https://www.cytodyn.com/investors/news-events/press-releases/detail/350/cytodyn-provides-update-on-dose-escalating-trial-with>

⁴⁸ <https://www.cytodyn.com/newsroom/press-releases/detail/405/treatment-with-cytodins-leronlimab-indicates-significant>

⁴⁹ <https://www.cytodyn.com/newsroom/press-releases/detail/402/fda-clears-cytodins-phase-2-randomized-trial-to-treat>

<p>VRC01 and VRC01LS</p> <p><i>Phase II</i></p>	<p>CD4 binding</p>	<p>VRC01 is an immunoglobulin G1 (IgG1) bNAb that targets the CD4 receptor site by binding to the HIV-1 envelope glycoprotein, thus blocking the entry of HIV-1 virus.⁵⁰ It is under development as a therapeutic vaccine (without the need of regular use of ART) and as a long acting formulation (VRC01LS) for PrEP.⁵¹</p> <p>VRC01 has been proven to be safe and well tolerated in HIV-positive^{52 53 54} and HIV-negative adult patients^{55 56}, when delivered intravenously or subcutaneously. VRC01LS also exhibited similar positive outcomes as an IV or SC injection in healthy HIV-1 uninfected adults.⁵⁷</p> <p>As the first proof-of-concept efficacy study, VRC01 is now being investigated in two Phase IIb PrEP Antibody Mediated Prevention (AMP) trials^{58 59}. Results are expected at the end of this year. It is also being clinically investigated as a combination with other bNAbs and for paediatric population.</p>
<p>VRC07, VRO7-523LS</p> <p><i>Phase II</i></p>	<p>CD4 binding</p>	<p>VRC07 is a next-generation engineered variant of VRC01 and also includes VRC07-523LS with approximately 5-8 times higher potency and an extended half-life, that targets the CD4 binding site.⁶⁰ A phase 1 dose-escalation clinical trial (PrEP) showed that VRC07-523LS was safe and well tolerated in healthy adults.^{61 62}</p> <p>A Phase II study to assess the safety, tolerability, PK, and antiviral activity of CAB LA (every 4 weeks) with VRC07-523LS (every 2 months) in virally suppressed patients was recently initiated.⁶³ Primary outcomes are expected by November 2021.</p> <p>Various other clinical trials are being conducted to explore the use of VRC07-523LS for treatment or for PrEP.</p>

PROCESS TECHNOLOGY FOR HIV TREATMENT

MPP also continues to explore whether there are opportunities for in-licensing patented technology that could contribute to improving manufacturing processes or reducing the manufacturing costs for medicines used for the treatment of HIV and opportunistic infections. This can relate to processes for the manufacturing of medicines under patent protection, for which MPP already has a licence, as well as those relating to older off-patent drugs.

LICENCE EXPANSION

Finally, MPP will also continue to explore opportunities to further expand its current licences so that additionally people may benefit from access to MPP-licensed products.⁶⁴

⁵⁰ Huang et al. (Apr 2020) JAIDS 83(4):434-439

⁵¹ <https://aidsinfo.nih.gov/drugs/603/vrc01/0/patient>

⁵² <https://clinicaltrials.gov/ct2/show/NCT02463227>

⁵³ <https://clinicaltrials.gov/ct2/show/NCT02411539>

⁵⁴ <https://clinicaltrials.gov/ct2/show/NCT01950325>

⁵⁵ <https://clinicaltrials.gov/ct2/show/NCT01993706>

⁵⁶ <https://clinicaltrials.gov/ct2/show/NCT02165267>

⁵⁷ <https://clinicaltrials.gov/ct2/show/NCT02599896>

⁵⁸ <https://clinicaltrials.gov/ct2/show/NCT02568215>

⁵⁹ <https://clinicaltrials.gov/ct2/show/NCT02716675>

⁶⁰ Rudicell et al. (2014) Journal of Virology 88(21):12669-82 doi: [10.1128/JVI.02213-14](https://doi.org/10.1128/JVI.02213-14)

⁶¹ Gaudinski et al. (2019) Lancet HIV, 6(10):PE667-E679 DOI: [https://doi.org/10.1016/S2352-3018\(19\)30181-X](https://doi.org/10.1016/S2352-3018(19)30181-X)

⁶² <https://clinicaltrials.gov/ct2/show/NCT03015181>

⁶³ <https://clinicaltrials.gov/ct2/show/NCT03739996>

⁶⁴ MPP currently holds licences on the following HIV medicines: abacavir (paediatric), atazanavir, bictegravir, cobicistat, dolutegravir, elvitegravir, lopinavir, ritonavir, tenofovir alafenamide and tenofovir disoproxil fumarate.

3. PRIORITIES IN HEPATITIS C

All the WHO-recommended medicines for the treatment of hepatitis C have already been licensed for use in LMICs either through MPP (daclatasvir, glecaprevir/pibrentasvir) or bilaterally by the patent holder (sofosbuvir, sofosbuvir/velpatasvir). Given that all candidate drugs that were previously in phase 2 clinical development have been discontinued by their sponsors, there are no new HCV medicines to be considered for prioritisation by MPP.

Nevertheless, MPP will continue to be active in hepatitis C in relation to:

- Facilitating development, availability, registration and uptake of its licensed medicines
- Exploring opportunities for further expanding the geographical scope of current licences⁶⁵
- Supporting the possible reformulation of glecaprevir/pibrentasvir as a long acting formulation, which could contribute to the development of a single-dose cure for hepatitis C (including under the Unitaaid-funded LONGEVITY project, more on this in section 5).⁶⁶
- Exploring whether MPP can play a role in facilitating broader access to other approved HCV medicines

4. PRIORITIES IN TUBERCULOSIS

TABLE 5 – SUMMARY OF PRIORITY TB DRUGS FOR MPP

TB DRUG	CLASS	MPP ANALYSIS
Bedaquiline (BDQ) <i>Phase III ongoing</i> <i>Registered with the US FDA and EMA</i>	Diarylquinoline	<p>As per the latest update from WHO in December 2019,⁶⁷ bedaquiline has now been recommended as part of a shorter all-oral injection-free regimen. This decision was taken on the basis of new data, including from the South African TB programme, which demonstrated that a shorter all-oral bedaquiline containing regimen safely improves patient outcomes when compared to a standardised shorter regimen with injectables.⁶⁸ The bedaquiline-containing BPaL regimen (bedaquiline, pretomanid and linezolid) has also been conditionally approved for patients with XDR-TB. As per the WHO update, the 2020 Consolidated Guidelines on treatment of drug-resistant TB will include use of bedaquiline for longer than 6 months and concurrent use of bedaquiline and delamanid. This confirms the growing clinical importance of bedaquiline in MDR-TB treatment.</p> <p>Following the end of the donation program in March 2019, the Global Drug Facility (GDF) now has an agreement with the originator whereby a course of bedaquiline can be procured by all countries who can purchase via the GDF at a price of USD 400.⁶⁹ It is expected that market entry of generics could lead to important price reductions.</p> <p>The compound patent on BDQ is expected to expire in 2023, with secondary patents expiring in 2025 and 2027. A licence has been granted to one company for the manufacture and supply of BDQ in Russia and certain other countries in the EECA region; reportedly, however, it is being sold at a higher price.⁷⁰ In countries with no secondary patents on BDQ, it is expected that generic manufacturers are likely to enter the market at that time, which will likely lead to price reductions in such countries. For other countries with secondary patents, generic market entry may need to wait until 2027. A licence on BDQ would enable faster market entry of quality assured generic version of this WHO-recommended treatment enabling further price reductions, under conditions that could require appropriate stewardship.</p>

⁶⁵ See recent announcement enabling more countries to access generic daclatasvir

⁶⁶ <https://unitaid.org/news-blog/unitaid-invests-in-long-acting-medicines-to-simplify-treatment-and-prevention-for-hiv-tb-malaria-and-hcv/#en>

⁶⁷ https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/

⁶⁸ <https://clinicaltrials.gov/ct2/show/NCT02454205>

⁶⁹ <http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp>

⁷⁰ <http://www.janssen.com/janssen-broadens-collaboration-russias-pharmstandard-advance-ongoing-efforts-tackle-multi-drug>

With respect to other recently approved medicines, an exclusive licence between Otsuka and Mylan on delamanid precludes the possibility of MPP obtaining a licence for the same indication, at least for as long as any exclusivity is in place. As a result, delamanid had been dropped from the list of MPP priorities in 2019 and this continues to be the case today.

In relation to pretomanid, it has limited IP protection in LMICs, with the compound patent having expired and patents on the combination with bedaquiline and linezolid still pending. Moreover, the TB Alliance (the innovator), has already entered into licensing agreements with generic manufacturers covering most LMICs.⁷¹

In addition, a number of TB candidate medicines have now proceeded to phase II. This is good news, as there are more new molecules in the clinical pipeline than there were until recently. They are mentioned below as part of an MPP watchlist in TB. Insufficient data is currently available for the full prioritisation of these compounds.

TABLE 6 – SUMMARY OF TB COMPOUNDS IN PHASE II DEVELOPMENT (MPP WATCHLIST)

TB DRUG CANDIDATE	CLASS	MPP ANALYSIS
Telacebec (Q203)	Imidazopyridine amide	Recent results from a Phase IIa Trial (in March 2020) ⁷² showed that increasing doses of telacebec resulted in greater reductions of bacterial load in sputum samples collected daily from 61 patients with newly diagnosed, rifampicin- and isoniazid-susceptible pulmonary tuberculosis. ⁷³ There were no serious adverse events reported. This proved that daily treatment with oral telacebec (100 to 300 mg) reduced the number of live TB bacteria in a dose dependent manner.
OPC-167832	3,4-dihydrocarbostyryl derivative	This compound is being developed in a phase I/II trial of multiple oral doses of OPC-167832 for uncomplicated pulmonary tuberculosis by Otsuka, in collaboration with the Bill and Melinda Gates Foundation. ⁷⁴ A recent publication from Otsuka has suggested that OPC-167832 in combination with 3-4 TB drugs has shown superior efficacy and prevented relapse compared to the standard treatment regimen. ⁷⁵
Delpazolid (LCB01-0371)	Oxazolidinone	Delpazolid is a new oxazolidinone with cyclic amidrazone synthesised by LegoChem BioSciences Inc. A phase II trial to evaluate early bactericidal activity, safety and pharmacokinetics ⁷⁶ was completed in February 2020, but full results have not yet been published. Interim results released at the 2019 TB Union Conference showed an average daily decline in TB bacterial count for multiple doses of Delpazolid. ⁷⁷
BTZ-043	Benzothiazinone	BTZ-043 is from a new class of drugs (benzothiazinones) and is currently being developed by the University of Munich and the German Center for Infection Research (DZIF). Results from Phase Ia Single Ascending Dose study proved BTZ-043 to be safe and well tolerated up to 500 mg. ⁷⁸ A new Phase Ib/IIa Multiple Ascending Dose study to evaluate the safety, tolerability, PK, drug-drug interaction and bactericidal activity of BTZ-043 (daily oral dose) administered over 14 days to 77 Drug Sensitive-TB participants was initiated in November 2019, with results expected by November 2020. ⁷⁹

⁷¹ <https://www.tballiance.org/news/tb-alliance-and-mylan-announce-global-collaboration-commercialize-investigational-drug> and <http://pharmabiz.com/News-Details.aspx?aid=119011&sid=2>

⁷² <https://www.businesswire.com/news/home/20200325005779/en/Orient-Announces-Publication-New-England-Journal-Medicine>

⁷³ <https://clinicaltrials.gov/ct2/show/NCT03563599>

⁷⁴ <https://clinicaltrials.gov/ct2/show/NCT03678688>

⁷⁵ <https://aac.asm.org/content/aac/early/2020/03/25/AAC.02020-19.full.pdf>

⁷⁶ <https://clinicaltrials.gov/ct2/show/NCT02836483>

⁷⁷ https://hyderabad.worldlunghealth.org/wp-content/uploads/2019/11/20191101_UNION2019_Abstacts_Final.pdf

⁷⁸ <https://clinicaltrials.gov/ct2/show/NCT03590600>

⁷⁹ <https://clinicaltrials.gov/ct2/show/NCT04044001>

GSK3036656 (GSK-070)	Oxaborole	GSK3036656 was found to be well tolerated in healthy adults as per the Phase I Single & Multiple Dose Ascending studies. ⁸⁰ A phase IIa study is now in progress for Drug Sensitive-TB patients with results expected in September 2020. ⁸¹
----------------------	-----------	---

5. LONG-ACTING FORMULATIONS IN HIV, HCV, TB AND MALARIA

In addition to the molecules listed above, MPP has recently begun to explore its role in facilitating the development of, and access to, new long-acting formulations that could be important in LMICs. As a first step, MPP will be exploring the licensing of promising new products whose development is being financed by Unitaid⁸². These are listed in Table 7.

TABLE 7 – PRIORITY LONG-ACTING TECHNOLOGIES/FORMULATIONS FOR IN-LICENSING

TECHNOLOGY HOLDER	PRODUCTS BEING DEVELOPED IN LONG-ACTING FORMULATION	ADDITIONAL DETAILS
Consortium led by the University of Liverpool ⁸³	Long acting formulations of: <ul style="list-style-type: none"> - Atovaquone - Rifapentine/isoniazid pro-drug - Glecaprevir/pibrentasvir based on ETFD technology	Based on their Emulsion-Templated Freeze Drying (ETFD) technology, ⁸⁴ the consortium led by University of Liverpool will formulate: <ul style="list-style-type: none"> - Atovaquone long-acting injectable (LAI) as a preventive therapy. - A combination of rifapentine and a prodrug of isoniazid to treat latent TB infection. - A long-acting injectable formulation of Glecaprevir/pibrentasvir that could provide options for test and cure strategy in a single curative dose. ETFD technology produces nano-to micro-particles of drug, to enable high drug masses to be suspended within lower volumes while maintaining the ability of the formulation to pass through an injection needle.

⁸⁰ <https://clinicaltrials.gov/ct2/show/NCT03075410>

⁸¹ <https://clinicaltrials.gov/ct2/show/NCT03557281>

⁸² [Global Health Panel: Opportunities to Address Global Health Challenges With Long-Acting Technologies, 3rd Long-acting injectables and implantables conference, Lalolla CA, Feb 6, 2020](#)

⁸³ <https://unitaid.org/project/long-acting-medicines-for-malaria-tuberculosis-and-hepatitis-c/#en>

⁸⁴ [Technologies utilised for LA drug delivery with a focus on Emulsion Templated Freeze Drying, Rannard S., 2nd Long-acting injectables and implantables conference, Leuven, Feb 7, 2019](#)

University of Washington ⁸⁵	Long-acting injectable of: Tenofovir/lamivudine/dolutegravir (TLD) based on DcNP technology ⁸⁶	Leveraging its novel “Drug combination Nanoparticle Platform” (DcNP) technology ⁸⁷ , the University of Washington aims to develop a composition of tenofovir/lamivudine/dolutegravir (TLD), WHO’s preferred first-line regimen ⁸⁸ , as an injectable to be administered once a month or once every three months.
MedinCell ⁸⁹	Long-acting ivermectin depot based on MedinCell’s BEPO® technology ⁹⁰	A long-acting ivermectin injectable formulation for vector control ^{91 92} based on MedinCell’s BEPO® technology. It would be administered once at the beginning of the malaria transmission season with an active duration of three months. The formulation uses the BEPO technology to form a fully bioresorbable depot once injected subcutaneously. Malaria vector mosquitoes are sensitive to ivermectin in the host bloodstream, as it reduces their fertility and survivorship or even induces their mortality. ⁹³ <small>94</small>

⁸⁵ <https://depts.washington.edu/tlcart/>

⁸⁶ <https://unitaid.org/project/long-acting-injections-to-treat-hiv/#en>

⁸⁷ <https://depts.washington.edu/tlcart/about/dcnpa-platform-validation/>

⁸⁸ https://www.who.int/hiv/pub/arv/DTG-TLD-arv_briefing_2018.pdf?ua=1

⁸⁹ <https://www.medincell.com/who-are-we/>

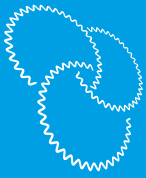
⁹⁰ <https://www.medincell.com/bepo/>

⁹¹ <https://unitaid.org/project/long-acting-medicines-for-innovative-vector-control/#en>

⁹² https://www.medincell.com/wp-content/uploads/2020/03/PR_MedinCell-Unitaid-EN_March2020.pdf

⁹³ Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety. Chaccour et al. *Malar J* 16, 161 (2017). <https://doi.org/10.1186/s12936-017-1801-4>

⁹⁴ [The effect of ivermectin on fertility, fecundity and mortality of Anopheles arabiensis fed on treated men in Ethiopia. Mekuriaw W, et al. *Malar J*. 2019 Nov; 8:18\(1\):357. doi: 10.1186/s12936-019-2988-3.](https://doi.org/10.1186/s12936-019-2988-3)



medicines
patent
pool

Rue de Varembé 7
1202 Geneva, Switzerland

www.medicinespatentpool.org