Pipeline Report » 2022

Long-Acting Technologies Trials Tracker for Hepatitis C, Opioid Use and Overdose Prevention Therapy, and Malaria

TAG
Treatment Action Group

Long-Acting Technologies Trials Tracker for Hepatitis C, Opioid Use and Overdose Prevention Therapy, and Malaria

By Joelle Dountio Ofimboudem

Edited by Bryn Gay, Annette Gaudino, Mark Harrington, Terri Wilder

The Unitaid-funded LONGEVITY project aims to develop long-acting formulations for malaria and latent tuberculosis (TB) prevention and a single-injection cure for hepatitis C virus (HCV) for low- and middle-income countries, as these diseases disproportionately affect children, poor and marginalized communities, people who use drugs, and people living with HIV. This trials tracker provides information on the development of long-acting HCV, malaria, and opioid use and overdose prevention therapy formulations and serves as a single reliable source for ongoing trials given the potential to use the same nanotechnology platform to produce a mass scale of different long-acting formulations.

As a partner in the Unitaid-funded LONGEVITY project, Treatment Action Group (TAG) supports the development of community surveys and ensures meaningful engagement with all stakeholders, including affected communities, civil society, research scientists, and medical providers, and the participation of these stakeholders in the development of these long-acting formulations. Community engagement and participation in the drug development process is critical to addressing barriers to demand creation and adoption of long-acting technologies. Effective community engagement in research and development (R&D) is predicated on strengthening the technical capacity of research-literate activists who follow the science; advocate for community perspectives on the research needs, treatment preferences, and acceptability in malaria, HCV, and TB to research scientists, governments, and key decision-makers; and report back to affected communities.

Long-acting formulations use nano-formulation processes to turn active pharmaceutical ingredients (or the raw materials of a medicine) into smaller "nano" particles, which enable a high mass to be turned into lower volumes that can be administered via syringe injections, patches, implants, or intravaginal rings providing sustained and gradual release of the active ingredient of a medicine. Once developed, long-acting formulations could potentially be administered weekly, monthly, or once every two or more months. This could provide alternatives to daily tablet/pill regimens, ensure more discretion for a person taking treatment, and help address stigma often associated with taking HCV and TB treatments. Long-acting preventives for malaria could contribute toward malaria control by prolonging the amount of time people remain malaria-free following administration. The development of long-acting medicines for HCV, malaria, as well as opioid use and overdose prevention therapy could add new drug delivery methods as part of a comprehensive toolbox for reaching global hepatitis and malaria elimination targets by 2030.

Long-Acting Formulations for Malaria

With respect to malaria, limited use of existing preventive measures such as insecticide-treated nets, indoor residual spraying, prevention chemotherapies, and misuse of prescription malaria medicines, have resulted in rising drug resistance to both preventative and treatment options, essentially rendering malaria control measures very ineffective in today's malaria endemic regions. Hence, the need to increase and diversify the malaria control toolbox. Newer preventative approaches such as the new malaria RTS,S/AS01 vaccine (Mosquirix), rolled out in 2021 following WHO recommendation—although only 38% effective and only available for children—and the long-acting injectable formulation for malaria prevention currently being developed under the LONGEVITY project all seek to diversify the malaria prevention and control toolbox to meet the malaria 2030 elimination targets.

Aside from adding to the malaria prevention and control toolbox, a long-acting formulation for malaria prevention will significantly contribute to achieving the malaria elimination targets set out in the WHO Global Technical Strategy for Malaria 2016–2030 and halt the rising resistance to malaria treatment in endemic regions. However, new approaches to delivering medicines through extended release would not be a panacea to addressing other health care barriers and social determinants of health.

Long-Acting Formulations for Hepatitis C Virus

To address the challenges associated with HCV treatment, long-acting technologies, which allow for the gradual and sustained release of the active ingredient of a medicine into the body over a period of time after administration, have the potential to ensure a discrete treatment option with one or two injections. By providing options for discrete treatment administration, long-acting formulations have the potential to address stigma, overcome challenges in accessing traditional medical facilities and pharmacies, improve treatment adherence, prevent relapses arising from treatment interruption, achieve more constant plasma levels in the blood during treatment, and simplify complex medication schedules.

Globally, only about nine countries (Australia, France, Iceland, Italy, Japan, South Korea, Spain, Switzerland, and the United Kingdom) are on track to achieving hepatitis elimination by 2030. This is mainly because HCV diagnoses remain very low in low- and middle-income countries, where only about 20% of people with chronic HCV infection know their status due to numerous barriers, including high costs for patients and multi-step diagnostic pathways—despite WHO guidelines recommending simplified diagnostics. Countries that have initiated hepatitis programs are reaching "diagnostic burnout," having treated previously diagnosed patients but scrambling to "find the missing millions" of undiagnosed people living with HCV. As a direct consequence, HCV treatment uptake, particularly in low- and middle-income countries, remains very low, with 80% of people with viral hepatitis lacking prevention, testing, and treatment services. Among the diagnostics and treatment challenges, stigma and discrimination deter people from seeking the cure and there are significant adherence challenges among people who are unstably housed, migrants, refugees, and people without consistent access to health care and social supports.

While we await the development of long-acting formulations in the research and development pipeline, evidence from the STORM-C SOF/RAV studies indicate the efficacy and safety of sofosbuvir and ravidasvir as an alternative HCV cure for patients with chronic hepatitis C infection without cirrhosis or with compensated cirrhosis. Developed by the Drug for Neglected Diseases Initiative, a nonprofit organization, SOF/RAV provides an additional cost-effective option for high burden, upper middle-income and low-income countries that still face treatment cost barriers.

Aside from developments in long-acting HCV treatment, researchers continue to explore possible preventive HCV vaccines (including using novel vaccine development platforms) given that prior infection does not prevent HCV reinfection. Also, the fact that 25% of people infected with HCV spontaneously clear the virus indicates that the immune system is capable of protecting us from HCV. According to researchers, possible avenues for vaccine development include immune response from people who have spontaneously cleared HCV and people at high risk of HCV who have repeatedly spontaneously cleared the virus. Following the failure of the first prophylactic HCV vaccine efficacy trial to prevent chronic infection, some of the key lessons learned from the research include the fact that vaccinating people when they are not at risk can harness a more robust immune response than after infection and that the immune systems of people who develop chronic HCV cross react with multiple genotypes and develop robust antibody responses. Also, following the recent findings on the exact nature of the interaction between HCV E2 and CD81 that allows HCV to enter and infect human cells, researchers believe that these new insights may provide the foundation for an HCV vaccine and new leads for developing the vaccine.

Long-Acting Medication for Opioid Use and Overdose Prevention

Long-acting buprenorphine, a medication for opioid use and overdose prevention that can be administered as a weekly or monthly injection, is part of a comprehensive set of tools for HCV prevention. Studies on the efficacy and safety of buprenorphine in reversing respiratory depression in methadone-poisoned opioid dependent patients suggest its potential use to reverse opioid overdose. Buprenorphine administration equally contributes to hepatitis elimination strategies by ensuring that people who use, quit, or safely inject drugs have different options for addressing or reducing their opioid use. Given that oral direct-acting antivirals (DAAs) for HCV cure have no drug-drug interactions with buprenorphine, it is possible that long-acting buprenorphine and a long-acting HCV cure may be administered together without adverse events.

Following the recent approval of long-acting cabotegravir (CAB-LA) administered as a single injection every eight weeks for HIV pre-exposure prophylaxis (PrEP) and cabotegravir/rilpivirine administered as a once-monthly or once every two months injection for HIV treatment, long-acting formulations have garnered a lot of interest from researchers and health advocates across the world. Aside from global pharmaceutical industry players, and thanks to the generous funding provided by Unitaid, more affordable long-acting formulations for HIV (under the University of Washington's GLAD project), HCV, TB, and malaria (under the LONGEVITY project) are being developed by research institutions in the United States and the United Kingdom. While this research is still in the preclinical stages, this updated trials tracker monitors current or completed studies on long-acting treatments for HCV, malaria, and opioid use and overdose prevention therapy.

The data are mainly derived from the U.S. clinicaltrials.gov and EU clinicaltrials.eu online registries and the International Clinical Trials Registry Platform (ICTRP) and its country-specific clinical trials registries.

The trial registry identifier numbers link directly to trial entries, which contain more detailed information on the trial design, enrollment criteria, principal investigators, and locations. Due to COVID-19, efforts to recruit people into ongoing studies may be paused or trials may be delayed. Communicate directly with the contact listed in the individual trial registry entries for current information about the status of the research. The data for this HCV, opioid use and overdose prevention therapy, and malaria trials tracker were compiled between May 16, 2021 and May 15, 2022, and will be updated on an annual basis. Please send updates, corrections, or suggestions to Joelle Dountio at jdountio@treatmentactiongroup.org.

	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Location	Phase	End Date	Published/ Presented Data
Malaria							
Repeat Ivermectin Mass Drug Administrations for Malaria Control II (RIMDAMAL II): a Double-blind, Cluster-randomized Control Trial for Integrated Control of Malaria	Injectable	NCT03967054 18-1803H	Brian Foy, Yale University, Institut de Recherche en Sciences de la Santé, Radboud University Medical Center, PATH	Burkina Faso	Phase 3	July 2023	Lancet. 2019 Apr 13; 393(10180): 1517–1526.
Adjunctive Ivermectin Mass Drug Administration for Malaria Control on the Bijagos Archipelago of Guinea Bissau: A Cluster-randomized Placebo-controlled Trial	Non-injectable	NCT04844905 19156	London School of Hygiene and Tropical Medicine, Medical Research Council Unit, The Gambia, Ministerio de Saude Publica Guinée-Bissau, Bandim Health Project, Instituto Nacional de Estudos e Pesquisas Guinée-Bissau	Guinea-Bissau	Phase 3	August 2023	N/A

	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Location	Phase	End Date	Published/ Presented Data
Chemoprevention With Monthly Intermittent Preventive Therapy (IPTp) With Dihydroartemisinin-piperaquine for Malaria in HIV-infected Pregnant Participants on Daily Cotrimoxazole in Kenya and Malawi: a Multi-centre Placebo-controlled Trial	Non-injectable	NCT04158713 17-005	Liverpool School of Tropical Medicine, Kenya Medical Research Institute, University of Malawi College of Medicine, Kenya National AIDS & STI Control Program, KEMRI-Wellcome Trust Collaborative Research Program, Centers for Disease Control and Prevention, University of Copenhagen, University of Cape Town, University of Massachusetts, Worcester, University of Toronto, University of Melbourne, CardiaBase	Kenya	Phase 3	November 2022	N/A
HCV							
Nothing new found							

	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Location	Phase	End Date	Published/ Presented Data
Opioid use and overdose prevention therapy							
Long-acting Buprenorphine vs. Naltrexone Opioid Treatments in Criminal Justice System-involved Adults	Injectable	NCT04219540 19-01450	NYU Langone Health, National Institute on Drug Abuse (NIDA)	USA	Phase 4	April 2024	J Subst Abuse Treat. 2021 Sep; 128: 108389.
Long Acting Subcutaneous Compared to Short Acting Sublingual Buprenorphine Administration in Pregnant and Lactating Women	Injectable The study compares the subcutaneous use and the sublingual use	NCT04212065 2019H0354	Ohio State University	USA	Phase 4 (withdrawn)	September 1, 2020	N/A
A Phase III, Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center Trial Assessing the Efficacy and Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) in Treatment of Adult Outpatients With Opioid Use Disorder	Injectable	NCT02651584 HS-11-421	Braeburn Pharmaceuticals	USA	Phase 3	November 2016	JAMA Intern Med. 2018 Jun1;178(6): 764-773.
An Open-Label Multicenter Study Assessing the Long-Term Safety of a Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injection Depot of Buprenorphine (CAM2038) in Adult Outpatients With Opioid Use Disorder	Injectable	NCT02672111 HS-14-499	Braeburn Pharmaceuticals	USA Australia Denmark Germany Hungary Sweden Taiwan United Kingdom	Phase 3	May 2017	Addiction. 2019 Aug; 114(8): 1416-1426.

	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Location	Phase	End Date	Published/ Presented Data
Phase II, Open-label, Partially Randomized, 3 Treatment Groups, Multi-Site Study Assessing Pharmacokinetics After Administration of the Once-Weekly and Once-Monthly, Long-Acting Subcutaneous Injectable Depot of Buprenorphine (CAM2038) at Different Injection Sites in Opioid-Dependent Subjects With Chronic Pain	Injectable	NCT02710526 HS-15-549	Braeburn Pharmaceuticals	United States	Phase 2	July 2017	https://clinicaltrials.gov/ct2/show/results/NCT02710526
CSP #2014 - Comparative Effectiveness of Two Formulations of Buprenorphine for Treating Opioid Use Disorder in Veterans (VA-BRAVE)	Injectable The study compares the subcutaneous use and the sublingual use	NCT04375033 2014	Veteran Affairs Office of Research and Development	United States	Phase 4	November 4, 2024	Addict Sci Clin Pract. 2022 Jan 31;17(1):6.
Long Acting Naltrexone for Opioid Addiction: the Importance of Mental, Physical and Societal Factors for Sustained Abstinence and Recovery	Injectable The study compares the subcutaneous use and the sublingual use	NCT03647774 2017-004706-18	Lars Tanum, Haukeland University Hospital, Hospital of Southern Norway Trust, The Hospital of Vestfold	Norway	Phase 4	December 2025	N/A
An Open-label, Multicentre, Single-arm Trial of Monthly Injections of Depot Buprenorphine in People With Opioid Dependence	Injectable	NCT03809143 CoLAB1801	The University of New South Wales	Australia		March 30, 2021	Int J Drug Policy. 2022 Feb;100:103492.

	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsor	Location	Phase	End Date	Published/ Presented Data
Long-acting Injectable Naltrexone Induction: A Randomized Trial of Outpatient Opioid Detoxification With Naltrexone vs. Buprenorphine	Injectable	NCT01377610 #6374/7250R	New York State Psychiatric Institute, National Institute on Drug Abuse (NIDA)	United States	Phase 1	December 2017	Am J Psychiatry. 2017 May 1;174(5):459-467.
Optimal Prevention of Overdose Deaths and Opioid Relapse Following Discharge: A Multi-Center RCT of Naltrexone Versus Buprenorphine in Norway	Non-injectable	NCT01717963 2011-002858-31	University of Oslo, The Research Council of Norway, The Royal Norwegian Ministry of Health, Norwegian Institute of Public Health, Oslo University Hospital, University Hospital Akershus, Haukeland University Hospital, Helse Stavanger HF, The Hospital of Vestfold, Ostfold Hospital Trust	Norway	Phase 3	April 2018	Am J Addict. 2021 Sep;30(5):453-460.