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Long-Acting Technologies for Hepatitis C and Malaria Trials Tracker

TAG
Treatment Action Group

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Long-acting drug delivery is an innovative method of administering drugs that allows for the gradual release of active ingredients into the body over a period of time. This drug delivery method has been revolutionary in contraception and in the treatment of psychological disorders such as schizophrenia. As early as 1952, long-acting injectable treatment for antipsychotics was developed as a strategy to improve treatment adherence, prevent relapses arising from treatment interruption, achieve more constant plasma levels in the blood, and simplify complex medication schedules.

The use of long-acting technology for preventing or treating HIV and opioid use disorder could be game-changing, working toward similar strategies of treatment adherence and simplification while also providing patients with discreet options and addressing treatment interruptions due to broken supply chains, particularly in low- and middle-income countries. These innovations use nanoformulation processes, which turn the active ingredients into smaller "nano" particles so a high mass can be held in lower volumes and passed through a small hole, such as an injection needle. Sustained release of a drug, administered by patches, implants, intravaginal rings, or injections, could be alternatives to daily pill regimens.

A long-acting formulation of cabotegravir has demonstrated safety and efficacy as a pre-exposure prophylaxis to prevent HIV in cisgender men and cis and trans women who have sex with men. A patient must take an oral lead-in, that is, an oral dose of cabotegravir, every day for five weeks before being given the long-acting cabotegravir as one injection every eight weeks. The oral lead-in period provides added safety to patients in case they have a reaction to the pills and before taking a long-acting injection. Additional data are being collected in open-label extension studies to understand if the oral lead-in can eventually be made optional. The U.S. Food and Drug Administration has approved a long-acting combination of cabotegravir/rilpivirine taken as a once-monthly shot to treat HIV, and an islatravir implant is being investigated as another long-acting HIV treatment. Long-acting buprenorphine, as weekly or monthly injections or as an implant given every six months to treat opioid use disorder, has been approved and in use in high-income countries since 2016 but may face patent-related barriers in low- and middle-income countries. Patients in one recent Australian study preferred long-acting buprenorphine to daily pills, indicating overall patient satisfaction, effectiveness, and ease of taking the treatment.

The long-acting treatment pipeline has expanded with the support of global funder Unitaid as part of efforts to redefine prevention and treatment of infectious diseases currently within its mandate. In 2020, Unitaid funded the development and commercialization of long-acting versions of medicines for the prevention and treatment of HIV, tuberculosis

(TB) infection, malaria, and the hepatitis C virus (HCV). The University of Liverpool will be developing long-acting preventives for malaria and TB, and a one-shot cure for HCV in the LONGEVITY project; the University of Washington's GLAD project reformulates dolutegravir into a long-acting HIV treatment taken once a month; and the MedinCell company's IMPACT project is developing a long-acting version of ivermectin to prevent malaria transmission. The projects aim to develop effective long-acting alternatives to the daily pills that are the standard of care for these diseases and improve adherence, clinical outcomes, and eventually costs. According to Unitaid, "moving from daily oral medication to weekly, monthly and less frequent long-acting formulations could accelerate efforts to control/end major global epidemics by improving patient adherence, containing resistance and reducing costs."

As a partner in the LONGEVITY project, TAG's role is to support the development of community surveys and ensure meaningful engagement with and participation of affected communities, civil society, research scientists, medical providers, and other stakeholders involved in the development of these long-acting formulations. Community engagement and participation in the drug development process is critical to addressing barriers to demand and adoption of long-acting technologies. Effective community engagement in R&D is predicated on strengthening the technical capacity of research-literate activists who follow the science; advocating community perspectives on the research needs and treatment preferences and acceptability in malaria, HCV, and TB to research scientists, governments, and key decision-makers; and report back to affected communities.

While the LONGEVITY trials are in pre-clinical stages, this Long-Acting Technologies Trials tracker monitors current or completed studies on long-acting treatments, namely for HCV and malaria. Clinical trials 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 HCV and malaria trial trackers were compiled between March 30 and May 15, 2021, and will be updated on an annual basis. Please send updates, corrections, or suggestions to Joelle Dountio at jdountio@treatmentactiongroup.org.

Table 1. Current Studies

Trial	Other Information	Trial Registry Identifier(s)	Manufac-turer/ Sponsors	Location(s)	Phase	End Date	Published/ Presented Data
Malaria							
Injectables							
IMPACT: Long-acting ivermectin	Used BEPO® technology for long-acting treatment for COVID-19	2020-001994-66; 2020-005015-40; 2020-001971-33; 2020-002091-12; 2020-001474-29; 2020-002283-32; 2021-000166-15 (COVID-19)	Unitaid; MedinCell		Phase I (COVID-19); Pre-Clinical (Malaria)	2023	Trop Med Int Health. 2020 Mar;25(3):380-6..

Table 2. Completed Studies

Long-acting injectables for HCV have been extensively studied during the pegylated-interferon era. The next chapter in long-acting injectables will investigate sustained release of direct-acting antivirals using new nanoformulation technologies.

Trial	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsors	Location(s)	Phase	End Date	Published/ Presented Data
Hepatitis C Virus							
Injectables							
GSK 2878175: Study to Assess Repeat Doses in Subject with Chronic Hepatitis C	Oral and injectable	NCT02014571	GlaxoSmithKline	Puerto Rico, USA	Phase I	January 2015	J Hep 2018 Jan;25(1):19-27.
Guard C: Global Observational Cohort Study on the Prediction of Adverse Effects in Patients Infected with Chronic Hepatitis C Receiving a Long-Acting Interferon Plus Ribavirin		NCT01344889	Hoffmann-La Roche	Albania, Algeria, Bahrain, Belgium, Bosnia and Herzegovina, Brazil, Egypt, Italy, Greece, Hungary, Kuwait, India, Islamic Republic of Iran, Italy, Lebanon, Morocco, Pakistan, Poland, Portugal, Qatar Lebanon, Republic of Korea, Republic of Macedonia, Romania, Serbia, Slovakia, United Arab Emirates	n.d.	June 2013	PLoS One. 2016 Mar 28;11(3):e0151703.
PLUS: An Open-Label Dose-Escalation Study to Assess Two Doses of LocteronTM (Poly ActiveTM - Interferon Alpha 2b) in Comparison with PEG-Intron		NCT00593151	Biolex Therapeutics, Inc.	USA	Phase I, II	March 2009	J Hepatol 2009; 50:S231 (abstract 628)

Trial	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsors	Location(s)	Phase	End Date	Published/ Presented Data
SELECT-2: Locteron Plus Ribavirin Comparison with PEG-Intron Plus in Patients with Genotype 1		NCT00863239	Biolex Therapeutics, Inc.	Bulgaria, Puerto Rico, Romania, USA	Phase II	November 2011	J Hepatol 2010; 52:S114 (abstract 272); J Hepatol 2011; 54:S181-182 (abstract 446); J Hepatol 2011; 54:S180-181 (abstract 444); Gastroenterol 2011; 140:S-942 (abstract su1868)
Malaria							
Injectables							
Seasonal Malaria Chemoprevention Versus a Long-Acting Artemisinin Combination Therapy for the Prevention of Malaria and Anaemia in Children	Preventive	NCT01651416	Centre for Global Health Research, Ghana; London School of Hygiene and Tropical Medicine	Ghana	Phase IV	July 2013	N/A
PMC Study: Dihydroartemisinin-piperaquine for Management of Severe Anaemia in Children Less Than 5 Years	Preventive	NCT02671175	Liverpool School of Tropical Medicine; The Research Council of Norway; Kenya Medical Research Institute; Makerere University	Kenya, Uganda	Phase III	December 2018	N Engl J Med. 2020 Dec 3;383(23):2242-2254; Trials. 2018 Nov 6;19(1):610.
Oral							
Kilimanjaro IPTi Drug Options Trial: Intermittent Preventive Treatment for Malaria in Infants in an Area with High Resistance to Sulfadoxine/ Pyrimethamine: an Evaluation of Short and Long-Acting Antimalarial Drugs	Preventive	NCT00158574	London School of Hygiene and Tropical Medicine; University of Copenhagen; National Institute for Medical Research, Tanzania; Kilimanjaro Christian Medical Centre, Tanzania	Tanzania	Phase III	June 2008	PLoS One. 2010 Mar 1;5(3):e9467; Lancet. 2009 Oct 31;374(9700):1521-32

Trial	Other Information	Trial Registry Identifier(s)	Manufacturer/ Sponsors	Location(s)	Phase	End Date	Published/ Presented Data
NECTAR2: Single Low Dose Tafenoquine to Reduce P. Falciparum Transmission (Malaria Transmission)		NCT04609098	London School of Hygiene and Tropical Medicine	Mali	Phase II		
Weekly Tafenoquine (WR 238605/SB252263) Compared to Mefloquine for Chemosuppression of Plasmodium Falciparum (Malaria Transmission)		NCT02488980	U.S. Army Medical Research and Development Command; SmithKline Beecham	Kenya	Phase II	March 2003	Travel Med Infect Dis. 2017 May-Jun;17:19-27.
Evaluation of Weekly Tafenoquine (SB 252263/WR 238605) Compared to Placebo for Chemosuppression of Plasmodium Falciparum (Malaria Transmission)		NCT02491606	U.S. Army Medical Research and Development Command; SmithKline Beecham	Kenya	Phase II	September 1998	Travel Med Infect Dis. 2017 May-Jun;17:19-27.
Evaluation of Increasing Doses of Weekly Tafenoquine for Chemosuppression of Plasmodium Falciparum (Malaria Transmission)		NCT02488902	U.S. Army Medical Research and Development Command; SmithKline Beecham	Ghana	Phase II	March 2003	Travel Med Infect Dis. 2017 May-Jun;17:19-27.
Evaluate Tafenoquine (SB252263) 300mg When Co-administered With the Artemisinin-based Combination Therapies (ACT) Artemether + Lumefantrine (AL) and Dihydroartemisinin + Piperaquine Tetraphosphate (DHA+PQP)		NCT02184637	GlaxoSmithKline; Medicines for Malaria Venture	USA	Phase I	April 2015	Antimicrob Agents Chemother. 2016 Nov 21;60(12):7321-7332.