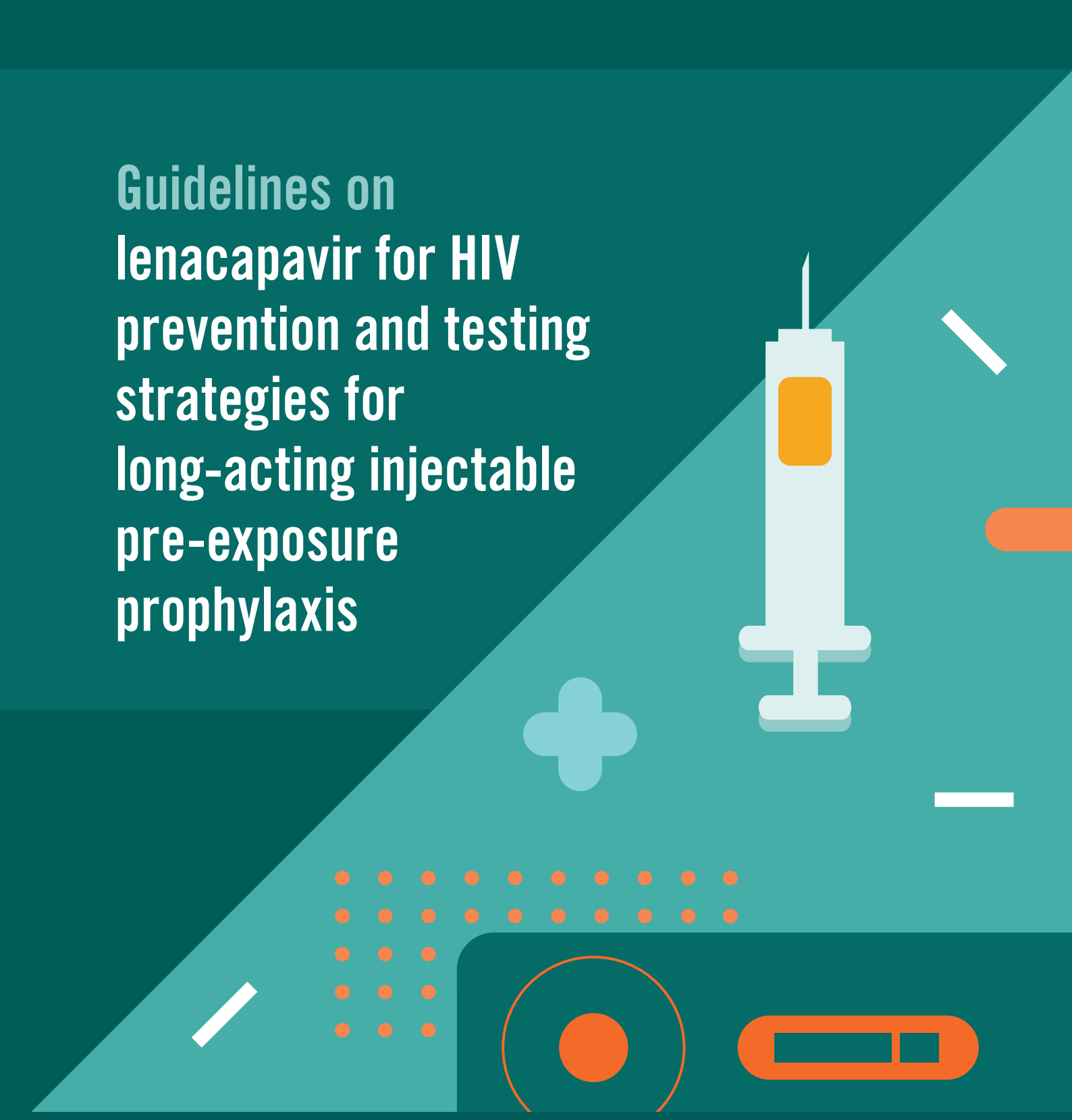
Guidelines on lenacapavir for HIV prevention and testing strategies for long-acting injectable pre-exposure prophylaxis



Web Annex G. Abstract: outcomes of lenacapavir administration during pregnancy

World Health Organization

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Abstract: Outcomes of lenacapavir administration during pregnancy

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Background. A review was conducted of the limited available data on the safety of lenacapavir (LEN) pre-exposure prophylaxis in pregnancy. LEN is the first-in-class HIV capsid inhibitor for prevention of HIV acquisition in cisgender women and for treatment of persons with multi-drug resistant HIV.

Methods. Review of published (Bekker et al., N Engl J Med 2024;391:1179-92) and unpublished data from Gilead Sciences (Moupali Das, personal communication, [7 January 2025]) on the safety of LEN in pregnancy.

Results: Pre-clinical studies of LEN in pregnant rabbits and rats found no significant effects on embryo–fetal or pre/postnatal fetal development at exposures (area under the curve) at doses 16 and 39 times, respectively, the exposure in humans at the recommended human dose. After administration to pregnant rats, LEN was detected in plasma of nursing pups, without ill effects.

The PURPOSE 1 phase III trial of LEN for HIV pre-exposure prophylaxis (PrEP) in cisgender women allowed women who became pregnant to stay on the study drug after consenting. There were 510 pregnancies in 487 women – 193 pregnancies on LEN, 219 on emtricitabine (F)/tenofovir alafenamide (TAF) and 98 on F/tenofovir disoproxil fumarate (TDF). At the time of the interim analysis, there were 277 pregnancy outcomes (105 LEN; 119 F/TAF; 53 F/TDF) and 233 pregnancies ongoing. Pregnancy complications were uncommon (3–4%) and did not differ between study groups. The rate of fetal demise was not significantly different between study groups or from the expected background rate in the populations studies; the rate of miscarriage was lowest in the LEN group (19%), compared with the F/TAF group (28.5%) and the F/TDF group (22.6%); the rates of stillbirth were 2.8%, 3.4% and 1.9%, respectively. There was one birth defect in the LEN group (1%), polydactyly in an infant with a family history of polydactyly. Thus, there was no sign of increased adverse pregnancy complications or birth outcomes with *in utero* exposure to LEN.

Since the interim analysis, there have been 289 additional pregnancies, with 115 occurring in LEN patients, which will give an estimated total of 308 pregnancy outcomes with LEN exposure when all pregnancy outcomes are available. More pregnancies are anticipated during the open-label extension of PURPOSE 1, which started in July 2024, with 94% of women opting to receive LEN. Pharmacokinetics studies of LEN in pregnancy and during lactation are ongoing and should be available in mid-2025.

Interpretation: While there are only a limited number of pregnancy outcomes to date, there is no sign of adverse pregnancy outcomes, including fetal loss or birth defects, with LEN exposure. With 200 preconception/first trimester exposures (current data cover 105 birth outcomes), we can rule out a 2-fold increase in risk of outcomes with a background rate of >10% (for example, miscarriage, prematurity, low birth weight) and those with a background rate of >3% (stillbirth, overall birth defects). More research and safety surveillance in pregnancy are needed to monitor for less common adverse pregnancy and infant outcomes, particularly rare adverse events, through the surveillance of PrEP use by larger surveillance programmes or antiretroviral pregnancy registries.

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