Title: Putting the ECHO results in context

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The ‘Evidence for Contraceptive Options and HIV Outcomes’ (ECHO) Trial Consortium found no statistically significant increase in HIV acquisition risk for women using intramuscular injectable depot medroxyprogesterone acetate (DMPA-IM) compared to those using the copper intrauterine device (IUD) or the levonorgestrol (LNG) implant.[1] In response, the WHO revised their medical eligibility criteria, which are used to develop counselling materials for women, to indicate that DMPA-IM should have no restriction on its use.[2] However, this decision does not adequately reflect the totality of evidence available.

First, interpreting trial results must be done in light of the study design. Ideally, DMPA-IM would have been compared to multiple contraceptive methods with non-inferiority determined between each method. In ECHO, DMPA-IM was compared to two other methods – which may or may not confer risk themselves – and was only powered to detect a hazard ratio (HR) ≥1·5 even though previous observational studies suggested lower effects (HR ~1.4).[3,4] The ECHO Consortium justified this design based on stakeholder consultation about a “meaningful difference that would inform policy change.”[1] Such a relativistic approach allows important absolute increases in risk conferred by a method to be overlooked. After all, a 20% increase in risk matters very much to a woman if her absolute risk is already high, and the HIV incidence of 3·81/100 woman-years in ECHO is well above the WHO’s threshold of “substantial” risk.[5] Mathematical modelling of this level of risk indicates that an extra 5,800 HIV infections could have occurred over the past five years in Uganda, a country with typical DMPA-IM use and HIV prevalence for sub-Saharan Africa. This is comparable to the number of infections pre-exposure prophylaxis (PrEP) might avert over the next five years in the same setting with typical short-term use. The situation may be more extreme in contexts like South Africa, where DMPA-IM use and HIV risk are both higher than in Uganda.

Secondly, we should be careful not to rely too much on the arbitrary threshold for *p*-values to indicate statistical significance, as highlighted in a recent commentary on ECHO.[6,7] Failing to find a statistically significant effect in a trial never implies evidence of no effect at all. We should be especially concerned about such inferences when the trial is underpowered, the trend is consistent with foregoing data, and the potential effect causes harm.

Therefore, we propose an interpretation of the ECHO result in the context of the wealth of other data, including observational, animal, and *in vitro* studies that have suggested a causal link between DMPA-IM and higher HIV acquisition risk.[3,4,8] One established way of synthesizing evidence is with a Bayesian perspective, whereby information about the true underlying risk would be modified, but not wholly determined by, new evidence. An heuristic example would be to use the observational evidence as a prior for the true HR, which when updated with the ECHO results and weighted towards the trial, might yield a posterior HR for DMPA-IM with a 95% credible range of 1·00-1·36. Regardless of the synthesis and weighting method, the appropriate interpretation is therefore not that the trial results obviated any possibility of risk, but only that our posterior estimate of the effect has been moderated. Women should have access to such a synthesis of data – which unfortunately includes this residual doubt of an effect – when making contraceptive choices. While there may be practical challenges involved with communicating nuanced messages about risk in resource-limited settings, this should not be a justification to misrepresent the evidence.

It is also useful to consider population-level HIV and reproductive health outcomes with different scenarios of future contraceptive use. We modelled four scenarios of changes in the contraceptive method mix relative to status quo in Uganda with potential HR values for DMPA-IM of 1·0-1·2 (figure; supplementary appendix). The model shows that, if women

stopped using DMPA-IM from 2019 onwards without replacement by other methods, the impact on reproductive health (maternal mortality and morbidity and mortality associated with unsafe abortions) would be detrimental irrespective of whether DMPA-IM really increased HIV risk: this scenario must be avoided. However, if other methods replace DMPA-IM, or overall contraceptive use is expanded, net health is improved regardless of DMPA-IM's precise increase in HIV risk. Thus, the best way to manage a residual and unknown risk for DMPA-IM is to ensure a greater diversity in the contraceptive method mix, give women comprehensive information about the risks, and improve access to effective contraception. This is the moment to increase women's choices and access to contraceptives, and not fall back to "business as usual."

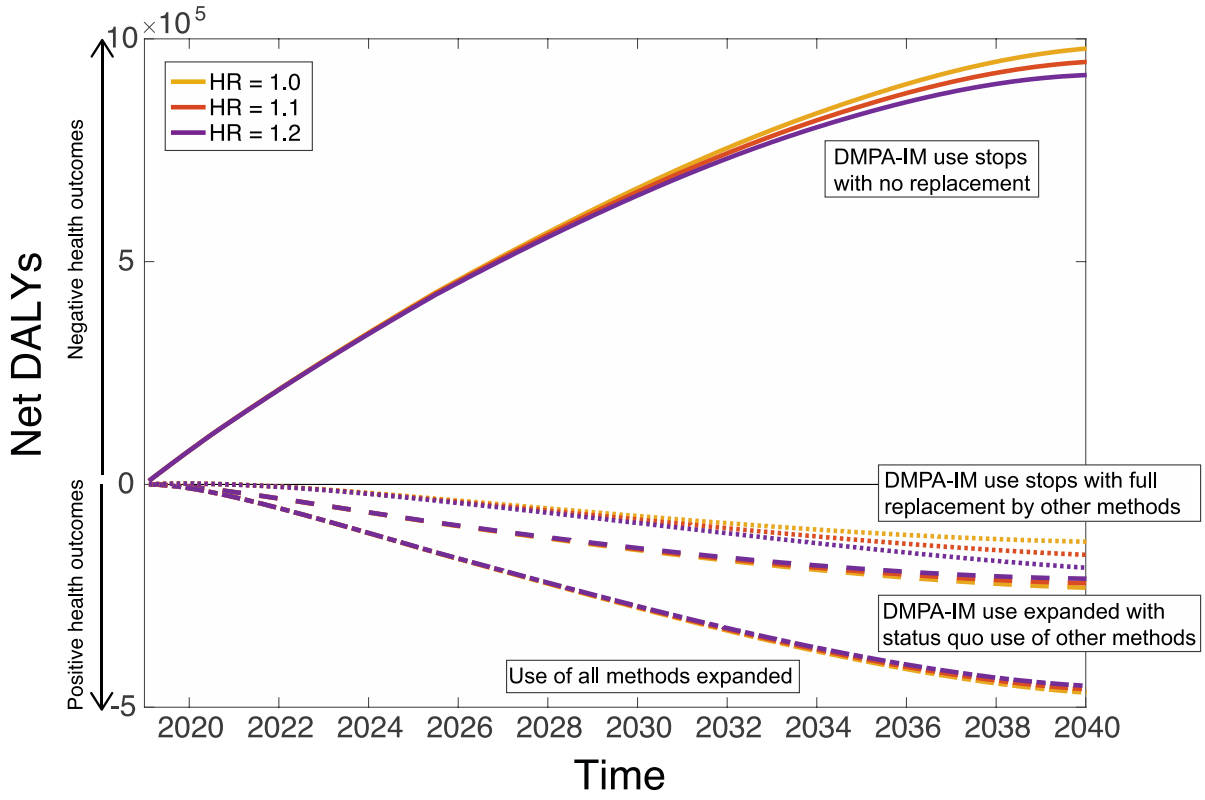

Figure: Net cumulative disability-adjusted life-years (DALYs) in Uganda from 2019-2040, with three hazard ratios (HR): 1.0 (yellow), 1.1 (orange), and 1.2 (purple) and four scenarios of DMPA-IM use from 2019 onwards: women stop using DMPA-IM with no replacement (solid lines; 15% overall contraceptive use among women 15-49), women stop using DMPA-IM with replacement of other contraceptive methods proportional to the method mix in 2019,

(dotted lines; 28% overall contraceptive use among women 15-49), DMPA-IM use is expanded (dashed lines; 33% overall contraceptive use among women 15-49), and all methods are expanded proportional to the method mix in 2019 (dashed and dotted lines; 42% overall contraceptive use among women 15-49). Results are compared to baseline scenarios of continued status quo DMPA-IM use (28% overall contraceptive use among women 15-49). DALYs include only HIV and reproductive health outcomes (maternal mortality and morbidity and mortality resulting from unsafe abortions), and do not include other known and potentially important health risks associated with oestrogen-containing methods, any complications of non-communicable diseases in pregnancy, any increased risk of sexually transmitted infections associated with any method use, morbidities associated with unsafe caesarean deliveries, or long-term co-morbidities associated with HIV infection.

Authors' contributions

BLJ and TBH drafted the initial version of the manuscript. JAS, NSP, JHHMvdW, ELG, HEJ, and LJR aided with interpretation and revising the content. All authors read and approved the final version of the manuscript.

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Conflicts of interest

Dr. Hallett reports grants from Bill & Melinda Gates Foundation during the conduct of the study. All other authors declare no conflicts of interest.

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