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The potential role of long-acting injectable cabotegravir–rilpivirine in the treatment of HIV in sub-Saharan Africa: a modelling analysis

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Summary

Background The use of a combination of the integrase inhibitor, cabotegravir, and the non-nucleoside reverse transcriptase inhibitor, rilpivirine, in a long-acting injectable form is being considered as an antiretroviral treatment option for people with HIV in sub-Saharan Africa. We aimed to model the effects of injectable cabotegravir–rilpivirine to help inform its potential effectiveness and cost-effectiveness under different possible policies for its introduction.

Methods We used an existing individual-based model of HIV to predict the effects of introducing monthly injections of cabotegravir–rilpivirine for people with HIV in low-income settings in sub-Saharan Africa. We evaluated policies in the context of 1000 setting scenarios that reflected characteristics of HIV epidemics and programmes in sub-Saharan Africa. We compared three policies for introduction of injectable cabotegravir–rilpivirine with continued use of dolutegravir-based oral regimens for: all individuals on antiretroviral therapy (ART); individuals with a recently measured viral load of more than 1000 copies per mL (signifying poor adherence to oral drugs, and often associated with drug resistance); and individuals with a recently measured viral load of less than 1000 copies per mL (a group with a lower prevalence of pre-existing drug resistance). We also did cost-effectiveness analysis, taking a health system perspective over a 10 year period, with 3% discounting of disability-adjusted life-years (DALYs) and costs. A cost-effectiveness threshold of US$500 per DALY averted was used to establish if a policy was cost-effective.

Findings In our model, all policies involving the introduction of injectable cabotegravir–rilpivirine were predicted to lead to an increased proportion of people with HIV on ART, increased viral load suppression, and decreased AIDS-related mortality, with lesser benefits in people with a recently measured viral load of less than 1000 copies per mL. Its introduction is also predicted to lead to increases in resistance to integrase inhibitors and non-nucleoside reverse transcriptase inhibitors if introduced in all people with HIV on ART or in those with a recently measured viral load of less than 1000 copies per mL, but to a lesser extent if introduced in people with more than 1000 copies per mL due to concentration of its use in people less adherent to oral therapy. Consistent with the effect on AIDS-related mortality, all approaches to the introduction of injectable cabotegravir–rilpivirine are predicted to avert DALYs. Assuming a cost of $120 per person per year, use of this regimen in people with a recently measured viral load of more than 1000 copies per mL was borderline cost-effective (median cost per DALY averted across setting scenarios $404). The other approaches considered for its use are unlikely to be cost-effective unless the cost per year of injectable cabotegravir–rilpivirine is considerably reduced.

Interpretation Our modelling suggests that injectable cabotegravir–rilpivirine offers potential benefits; however, to be a cost-effective option, its introduction might need to be carefully targeted to individuals with HIV who might otherwise have suboptimal adherence to ART. As data accumulate from trials and implementation studies, such findings can be incorporated into the model to better inform on the full consequences of policy alternatives.

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possibility of injectable cabotegravir–rilpivirine use in sub-Saharan Africa.³ Potential advantages of injectable forms over current oral regimens are that injections result in adequate drug concentrations for a 1–2 month period, without dependence on adherence to daily oral pill taking. Disadvantages include cabotegravir appearing to have a lower barrier to resistance than does dolutegravir;⁴ a long so-called tail of cabotegravir drug concentrations if combination treatment is stopped, which might lead to selection of drug resistance if other antiretroviral drugs are not taken, potentially risking class-wide integrase strand transfer inhibitor resistance;⁵ injections might be painful and induce injection-site skin reactions; and the possibility of higher costs with injectables forms than with oral therapy for procurement and delivery, as well as a greater time commitment for clinic staff. Studies of implementation of injectable cabotegravir–rilpivirine in low-income settings in sub-Saharan Africa might be guided usefully by modelling exercises exploring potential effects in different subpopulations. We aimed to model the effects of injectable cabotegravir–rilpivirine on ART outcomes in patients with HIV from these settings and to assess its cost-effectiveness to help to inform potential policies for its introduction.

Methods

Modelling approach

The HIV synthesis model is an individual-based simulation model that has been described in detail elsewhere.²¹ Each time the model programme is run, it creates a simulated dataset of attributes of a population of adults from 1989 (the notional start date of the HIV epidemic), with updates every month (adapted from 3 months for this exercise) on variables including age, sex, presence of a primary condomless sex partner and number of short-term condomless sex partners, HIV testing, male circumcision, use of pre-exposure prophylaxis and, for HIV-positive people, time from infection, CD4 cell count, viral load, specific antiretroviral drugs being used, antiretroviral drug adherence (for oral drugs), and specific drug resistance mutations. In this analysis, adherence refers to the extent of optimal pill taking as prescribed in the 1 month period among people who are attending clinic. ART interruption is modelled separately. Adherence to the specific drugs being taken and the presence of drug resistance mutations jointly determine the current amounts of suppressive antiviral effect of the regimen at any point in time. Through sampling of several parameter values, we create a series of so-called setting scenarios reflecting uncertainty in assumptions and a range of characteristics similar to those seen in southern and east Africa. For example, we sample parameters relating to rates of HIV testing; linkage and retention; adherence to oral antiretroviral drugs; resistance emergence, transmission, and persistence; ART interruption; extent of implementation of viral load monitoring; and rate of switching to second-line therapy after detected virological failure. A table of parameters and the criteria for a setting scenario to be accepted are provided in the appendix (pp 2–10). With our setting scenarios, we aim to reflect subsettings within countries, not just countries in aggregate.

For each setting scenario, we randomly sampled injectable cabotegravir–rilpivirine introduction policies, modelling transition to injectable cabotegravir–rilpivirine for three groups: first, all people on ART; second, people with a most recently measured viral load of more than 1000 copies per mL (as a means of selecting people with a tendency for poorer adherence to oral drugs); and third, people with a recently measured viral load of less than 1000 copies per mL (a group with a lower prevalence of pre-existing drug resistance).
Context
We assumed a context where dolutegravir was introduced over 2019–20 and where all people on ART were switched to tenofovir disoproxil fumarate–lamivudine–dolutegravir. If there were two viral load values above 1000 copies per mL on this regimen, it was switched to boosted protease inhibitor plus zidovudine and lamivudine. We further assumed that viral load monitoring was in place, but with varying levels of implementation across setting scenarios.

Cost-effectiveness analysis
Outcomes compared include the proportion of people on ART with viral suppression, AIDS-related deaths, disability-adjusted life-years (DALYs), and net DALYs (which account for costs of a policy on the basis of a cost-effectiveness threshold of US$500 per DALY averted). The cost-effectiveness threshold should reflect the health gains that could have been delivered through other interventions that can no longer be provided if the evaluated interventions are funded (ie, the health opportunity costs). HIV care in sub-Saharan Africa is mainly funded by external development assistance; therefore, this is unlikely to depend as much on a country’s income level for HIV spending as for general health care. Although uncertain, $500 averted per DALY is likely to be at the upper end for lower-income countries in the region, on the basis of evidence concerning how resources could otherwise be used. Incremental cost-effectiveness ratios for funded interventions such as the expansion of ART to every patient with diagnosed HIV, which includes an increased need for testing and use of viral load monitoring, are around this value. Given the discussions around feasibility of implementation at the time of adoption, these appear to be on the borderline of cost-effective interventions. Furthermore, for South Africa, a middle-income country that funds most of its programme through domestic funding, a cost-effectiveness threshold of $750 has been proposed because this is approximately the cost per life-year averted of HIV interventions at the borderline for inclusion within the South African HIV Investment Case, which prioritises use of the national HIV budget on the basis of intervention cost-effectiveness.1

The cost of tenofovir disoproxil fumarate–lamivudine–dolutegravir, including the supply chain, is assumed to be $78 per patient per year.10 The cost at which injectable cabotegravir–rilpivirine could be delivered is unknown and we initially use a cost of $120 per patient per year for illustrative purposes only, which includes all costs associated with its delivery, including that of the drug and supply chain, and any additional costs in the clinic beyond those required in the context of current oral drug use. Costs of providing clinic visits in the context of current oral drug use ($80 per patient per year unless viral load is known to be suppressed, in which case $40 per year; we make no explicit assumptions on prescription lengths for tenofovir disoproxil fumarate–lamivudine–dolutegravir) and viral load testing ($22 per test) are considered separately from these costs. Absolute numbers of health-related events, costs, and DALYs are relevant for a population with a size of approximately 10 million adults in 2020. The cost-effectiveness analysis was done from a health-care perspective, with costs and health outcomes both discounted to present $ values at 3% per annum. Other unit costs and disability weights are described in the appendix (pp 11–12).

Modelling drug resistance
Before explaining how we modelled injectable cabotegravir–rilpivirine, we first describe how we modelled the effects of oral drug regimens. For an individual on oral ART in the model, the risk of new drug resistance mutations arising depends on their adherence in the current month, which is modelled as a percentage between 0% and 100% full adherence. People with an adherence of less than 80% in a given month have a substantially higher risk of drug resistance than those with an adherence of 80% or above. Risk of resistance mutations is drug-specific, but the relative rate of resistance between individuals with at least 80% adherence and those with less than 80% adherence is assumed to be the same across drugs. These assumptions have been previously shown to lead to levels of drug resistance consistent with observed data.8,15 People have a long-term average tendency to adhere to oral drugs, but there is variability within individuals by month. The current amount of activity of the overall regimen is the sum of the activity of each drug in the regimen, accounting for the intrinsic drug potency and the current level of resistance to the drug, in which the potency conveys the contribution of a drug to the antiviral activity of a regimen against a virus with no resistance, informed by early short-term studies of drugs in development used as monotherapy and inferred from the potency of regimens of drug combinations.8,10 People can interrupt oral drugs and, if so, there is a high probability that this coincides with a stop in clinic attendance. In people with low long-term tendency to adhere to ART, there is an increased rate with which such interruption can occur. With the inclusion of long-acting injectable drugs, we generalised the adherence percentage to be thought of as a measure of the degree to which concentrations of the drugs being taken are optimal in the 1 month period. Where the percentage is above 80%, we referred to this as indicating optimal drug concentrations for the month; where it is below 80%, we referred to such as indicating suboptimal drug concentrations. We assumed that injections are monthly.

We modelled indicative non-nucleoside reverse transcriptase inhibitor mutations at reverse transcriptase codon positions 101, 103, 138, 181, 188, and 190. The risk
of resistance mutations with rilpivirine is higher than with efavirenz. We accounted for the fact that there is cross resistance between efavirenz and rilpivirine, although rilpivirine remains active in the presence of the Lys103Asn mutation. The risk of integrase inhibitor mutations (Gln148 or Arg263 are the major integrase inhibitor mutations considered) is two times higher with dolutegravir, and cabotegravir are assumed to have the same potency and this is set to 1·5 or 2·0 (determined by sampling for each run), and 2·0 for atazanavir and lopinavir.

Cabotegravir has a long half-life and, if no further injections or oral drugs are taken, the cabotegravir–rilpivirine concentration after the most recent injection is assumed to remain above 80% of optimal drug concentration for 2 months (ie, at low-resistance risk) and then fall to a suboptimal concentration (ie, at high-resistance risk) for the following 3, 6, or 12 months. The suboptimal concentration period of 3, 6, or 12 months is variable across individuals. During this period, there is some antiviral effect of the regimen. The potency of each drug (the activity amount if no resistance mutations considered) is two times higher with efavirenz, rather than the two being the same (33% of setting scenarios). Additionally, people with lower adherence might tend to correspond to individuals with lower levels of sexual transmission risk (20% of setting scenarios).

Role of the funding source
The programme officers for the funder (GPG and PE) had input into the modelling design and are coauthors on this report as a result of their input and expertise. The funder of the study had no other role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Table 1 shows the characteristics of the population in July, 2020, across 1000 setting scenarios, with observed values from sub-Saharan African countries provided for context, although we note that we aimed for our setting scenarios to also reflect the range of epidemic characteristics in specific subsettings within countries.

Table 2 shows the predicted effects of the introduction of injectable cabotegravir–rilpivirine compared with oral antiretrovirals, rather than the two being the same (33% of setting scenarios). Additionally, people with lower adherence might tend to correspond to individuals with lower levels of sexual transmission risk (20% of setting scenarios).
lead to an increase in the proportion of people on ART who have viral load suppression and a decrease in AIDS-related deaths, compared with no introduction. Its introduction was also predicted to lead to increases in integrase inhibitor and non-nucleoside reverse transcriptase inhibitor resistance, if introduced in every patient on ART or in individuals with a recently measured viral load of more than 1000 copies per mL, but not in those with viral loads of more than 1000 copies per mL. This effect is due to the fact that use of injectable cabotegravir–rilpivirine is concentrated among people with reduced adherence to oral therapy, who would carry a risk of integrase inhibitor resistance with oral therapy. Consistent with the effect on AIDS-related mortality, all approaches to the introduction of injectable cabotegravir–rilpivirine were predicted to avert DALYs.

With our assumed indicative cost of $120 per person per year for injectable cabotegravir–rilpivirine, overall programme costs were predicted to increase substantially with the policy for every patient on ART or for individuals with a viral load of less than 1000 copies per mL, but to a much lesser extent with the policy for those with a viral load of more than 1000 copies per mL (table 2). This difference is due to the targeting to people who are more costly to manage because of, for example, the high costs of second-line protease inhibitor-based regimens. Net DALYs are averted with the injectable cabotegravir–rilpivirine policy for those with a viral load of more than 1000 copies per mL.
1000 copies per mL. The introduction of such a regimen for this patient group was cost-effective in 59% (95% CI 53–64) of setting scenarios (table 3). Other policies for the introduction of injectable cabotegravir–rilpivirine were not cost-effective. These findings are based on our assumed cost of $120 for this regimen per person per year. We also asked the question of what the maximum cost of delivering injectable cabotegravir–rilpivirine would be for the introduction of the regimen’s policy for individuals with a viral load of more than 1000 copies per mL to be cost-effective (ie, for the mean net DALY averted to be ≥0). We found such cost to be $131 per person per year.

In further analyses (based on the cost of $120 per person per year for injectable cabotegravir–rilpivirine), we considered the effects of restricting setting scenarios in various ways on the percentage of scenarios in which a policy for the regimen in people with a recently measured viral load of more than 1000 copies per mL is cost-effective (table 3).

### Discussion

We did an exploratory modelling analysis to inform potential ways in which the introduction of injectable cabotegravir–rilpivirine could have a beneficial effect on ART outcomes in patients with HIV in sub-Saharan Africa. We found that this regimen could have a substantial positive effect if targeted to patients with a viral load of more than 1000 copies per mL (despite being on a tenofovir disoprophyl fumarate–lamivudine–dolutegravir regimen), a group for whom adherence to pill taking is more likely to be suboptimal. Delivered at a cost of below $131 per person per year, injectable cabotegravir–rilpivirine is potentially cost-effective when used in this group. In individuals with a viral load of more than 1000 copies per mL on a tenofovir disoprophyl fumarate–lamivudine–dolutegravir regimen, there is likely to be a considerable risk of integrase inhibitor resistance. Use of injectable cabotegravir–rilpivirine instead of the oral regimen is not predicted to result in any higher risk. Although increasing viral load suppression and reducing DALYs, the increased overall costs associated with use of injectable cabotegravir–rilpivirine in every patient on ART or in those with a viral load of less than 1000 copies per mL outweigh the benefits under our assumptions.

We note that the consequences of increased implementation complexity (including cold chain, syringes, coadministration of two separate products, the possible need for an oral cabotegravir–rilpivirine dose lead-in to rule out serious toxicity, a need to rule out hepatitis B before stopping tenofovir, a need to move away from injectable cabotegravir–rilpivirine during treatment for active tuberculosis, the burden on the patient of monthly clinic visits) and time inputs in clinics required with the monthly delivery of injectable cabotegravir–rilpivirine are not fully known yet. On the basis of our current assumptions, the cost associated with these factors would need to be considered within the proposed $131 per person per year ceiling cost. Injections once every 2 months rather than once every month partially reduces some of these costs. Additionally, some programmes are not able to carry out monitoring of viral load annually as most guidelines propose; therefore, this limits the ability to implement the policy we modelled.

Subpopulations that might be most susceptible to chronic poor adherence to daily oral drugs include adolescents and young adults (aged <20 years), and mobile workers who might have a particular aversion to carrying pills. Individuals who might benefit the most might also be those with highest sexual risk behaviour. These patients might be the subpopulations in whom injectable cabotegravir–rilpivirine is first introduced. We considered targeting injectable cabotegravir–rilpivirine

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**Table 3: Sensitivity analyses showing percentage of setting scenarios in which injectable cabotegravir–rilpivirine is cost-effective in people with a recently measured viral load of >1000 copies per mL.**

| Percentage of cost-effective setting scenarios | Overall 59% (53–64) |
|-----------------------------------------------|----------------------|
| Time cabotegravir is at suboptimal concentrations after last injection |
| 3 months in 70% of people, 6 months in 20% |
| 1 year in 10% |
| 3 months in 33% of people, 6 months in 33% |
| 1 year in 33% |
| 3 months in 10% of people, 6 months in 20% |
| 1 year in 70% |

**Table 3: Sensitivity analyses showing percentage of setting scenarios in which injectable cabotegravir–rilpivirine is cost-effective in people with a recently measured viral load of >1000 copies per mL.**

| Percentage of all people with HIV who have a viral load of >1000 copies per mL at baseline* |
|-----------------------------------------------|
| Highest tertile (>70%) 45% (36–55) |
| Lowest tertile (<50%) 69% (60–78) |

**Table 3: Sensitivity analyses showing percentage of setting scenarios in which injectable cabotegravir–rilpivirine is cost-effective in people with a recently measured viral load of >1000 copies per mL.**

| Percentage of people on ART who are on a second-line (protease inhibitor-based) regimen at baseline |
|-----------------------------------------------|
| Highest tertile (>10%) 81% (72–87) |
| Lowest tertile (<5%) 39% (30–48) |

Data are % (95% CI). Baseline refers to 2020. Effects are compared with those of an active tuberculosis, the burden on the patient of monthly clinic visits) and time inputs in clinics required with the monthly delivery of injectable cabotegravir–rilpivirine are not fully known yet. On the basis of our current assumptions, the cost associated with these factors would need to be considered within the proposed $131 per person per year ceiling cost. Injections once every 2 months rather than once every month partially reduces some of these costs. Additionally, some programmes are not able to carry out monitoring of viral load annually as most guidelines propose; therefore, this limits the ability to implement the policy we modelled.

Subpopulations that might be most susceptible to chronic poor adherence to daily oral drugs include adolescents and young adults (aged <20 years), and mobile workers who might have a particular aversion to carrying pills. Individuals who might benefit the most might also be those with highest sexual risk behaviour. These patients might be the subpopulations in whom injectable cabotegravir–rilpivirine is first introduced. We considered targeting injectable cabotegravir–rilpivirine
according to recent viral load; however, implementation studies might consider other direct measures of adherence, such as measurement of drug concentrations.

We are mindful that selection of people based on increased viral load means that we are likely to select a group among whom levels of drug resistance are high, and our proposed policy does not include any drug resistance testing to detect this given that, until now, such testing has not been feasible for programmes. Our modelling attempts to take this into account and the predicted benefits of the policy are in this context. However, such a policy might be viewed as a clinically unacceptable approach nevertheless.

Given that a high proportion of people might consider injectable cabotegravir–rilpivirine as a convenient option, a policy of introducing the regimen only in patients with a viral load of more than 1000 copies per mL could lead to an incentive of poor adherence to oral drugs in individuals who wish to access the injectable form; therefore, the approach to implementation would have to be carefully considered. Because a person with close to 100% adherence to oral drugs is likely to have a lower risk of resistance with tenofovir disoproxil fumarate–lamivudine–dolutegravir than with injectable cabotegravir–rilpivirine, if given this information by clinical staff, patients could effectively self-select to use injectable cabotegravir–rilpivirine if they have concerns over their ability to sustain adherence to oral drugs. By contrast, those patients who are confident in their ability might prefer the reassurance of a predicted very low risk of resistance development. In practice, the approach tested for provision of injectable cabotegravir–rilpivirine might be based on allowing people to make an informed choice. It will be important to run such pilot programmes to see how use plays out. Our modelling results imply that such an approach is unlikely to be cost-effective at the drug costs and dosing regimen considered; however, uncertainty remains and our modelling should be updated when data on actual programme experience are available.

We considered whether our conclusions were affected by plausible variations between setting scenarios or by uncertainty over assumptions. Most notably, we found that the policy was less likely to be cost-effective in the context of programmes in which the proportion of people on ART who had a viral load of less than 1000 copies per mL was higher. We also found that the policy was more likely to be cost-effective in settings in which there was a higher proportion of people on second-line ART. This finding probably reflects that, due to the high cost of second-line regimens, the benefits provided by injectable cabotegravir–rilpivirine in achieving higher levels of viral suppression are greater.

A 2020 modelling study considered the minimum additional cost of injectable cabotegravir–rilpivirine, compared with oral therapy, for this regimen to be considered a cost-effective option in adolescents in Kenya.7 Using the same $500 per DALY averted cost-effectiveness threshold as in our study, the authors found that an additional annual cost of up to $89 beyond the cost of oral treatment could be possible. Although in a somewhat different context, this cost is not far from the equivalent figure of $53 for our study ($131–$78 for tenofovir disoproxil fumarate–lamivudine–dolutegravir).

Modelling can help to combine the pieces of information available, making assumptions as necessary and exploring the effect of these assumptions. This approach helps to establish what the potential effects of policy options and their cost-effectiveness could be, but it does not provide empirical data in the way that a randomised trial does, and it is important that this difference is understood. The main limitation of this work is uncertainty over many of the assumptions, particularly related to injectable cabotegravir–rilpivirine, because it is yet to be introduced into clinical practice.

In conclusion, our modelling suggests that injectable cabotegravir–rilpivirine offers potential benefits to patients with HIV on ART in low-income settings in sub-Saharan Africa; however, its introduction would probably need to be carefully targeted if it is to offer a cost-effective option, and much uncertainty remains. As data accumulate from trials and implementation studies, such findings can be incorporated into the model to better inform on the full consequences of policy alternatives.

Contributors
All authors contributed to model development, and the conception, specific modelling of long-acting injectables, or both. ANP ran the model and drafted the manuscript. All authors had critical input in drafting the manuscript. ANP, LB-M, and VC had full access to the model programme.

Declaration of interests
CWF reports personal fees from Merck, Mylan Pharmaceuticals, ViViD Healthcare, Gilead Sciences, and Algenon Pharmaceuticals, outside of the submitted work. CWF also has an issued patent for semi-solid prodrug solid drug nanoparticles and for anhydrous nanoprecipitation for the preparation of nanodispersions of tenofovir disoproxil fumarate in oils as candidate long-acting injectable depot formulations. SP reports grants from Gilead Sciences, ViViD Healthcare, Janssen-Cilag, and European and Developing Countries Clinical Trials; and salary support from Medical Research Council grant (MC_UU_12023/23) (MC_UU_12023/26), outside of the submitted work. CWF also has an issued patent for semi-solid prodrug solid drug nanoparticles and for anhydrous nanoprecipitation for the preparation of nanodispersions of tenofovir disoproxil fumarate in oils as candidate long-acting injectable depot formulations. SP reports grants from Gilead Sciences, ViViD Healthcare, Janssen-Cilag, and European and Developing Countries Clinical Trials; and salary support from Medical Research Council grant (MC_UU_12023/23) (MC_UU_12023/26), outside of the submitted work. PE and GPG were programme officers for the funder and had input into the modelling design. All other authors declare no competing interests. This Article is based on research funded by the Bill & Melinda Gates Foundation. The findings and conclusions contained within are those of the authors and do not necessarily reflect the official positions or policies of the Bill & Melinda Gates Foundation.

Data sharing
The model programme is available on figshare.

References
1 WHO. Update of recommendations on first- and second-line antiretroviral regimens. Geneva: World Health Organization, 2019.
2 Margolis DA, Gonzalez-Garcia J, Stellbrink H-J, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2) : 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet 2017; 390: 1499–510.

3 Swindells S, Andrade-Villanueva J-F, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. N Engl J Med 2020; 382: 112–23.

4 Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. N Engl J Med 2020; 382: 1124–35.

5 Silja Fröhlich, Alex Gitta. Uganda finalizes research on injectable HIV drug. March 3, 2020. https://www.dw.com/en/uganda-finalizes-research-on-injectible-hiv-drug/a-52623804 (accessed Feb 10, 2021).

6 Oliveira M, Ilanescu RI, Anstett K, et al. Selective resistance profiles emerging in patient-derived clinical isolates with cabotegravir, bictegravir, dolutegravir, and elvitegravir. Retrovirology 2018; 15: 56.

7 Zhang WW, Cheung PK, Oliveira N, Robbins MA, Harrigan PR, Shahid A. Accumulation of multiple mutations in vivo confers cross-resistance to new and existing integrase inhibitors. J Infect Dis 2018; 218: 1773–76.

8 Phillips AN, Bansi-Matharu L, Venter F, et al. Updated assessment of risks and benefits of dolutegravir versus efavirenz in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines. Lancet HIV 2020; 7: e193–200.

9 Phillips A, Cambiano V, Johnson L, et al. Potential impact and cost-effectiveness of condomless-sex-concentrated PrEP in KwaZulu-Natal accounting for drug resistance. J Infect Dis 2019; published online Dec 18. https://doi.org/10.1093/iridis/jiz667.

10 Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. March 2015. https://www.york.ac.uk/media/che/documents/papers/researchpapers/CHERP109_cost-effectiveness_threshold_LMICs.pdf (accessed Nov 1, 2018).

11 Eaton JW, Menzies NA, Stower J, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. Lancet Glob Health 2014; 2: e23–34.

12 Phillips A, Shroufi A, Vojnov L, et al. Sustainable HIV treatment in Africa through viral-load-informed differentiated care. Nature 2015; 528: 568–76.

13 Meyer-Rath G, Jamieson L, Chiu C, et al. Optimising South Africa’s HIV response: results of the HIV investment case. International AIDS Economic Network; Durban; July 15–16, 2016.

14 Clinton Health Access Initiative. The state of HIV treatment, testing, and prevention in low- and middle-income countries. Sept 20, 2019. https://www.clintonhealthaccess.org/the-state-of-the-hiv-market-in-low-and-middle-income-countries-2/ (accessed Feb 10, 2021).

15 Phillips AN, Venter F, Hlavin D, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV 2019; 6: e116–27.

16 Cohen CJ, Molina J-M, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two phase III randomized trials. AIDS 2013; 27: 939–50.

17 Culhane J, Sharma M, Wilson K, et al. Modeling the health impact and cost threshold of long-acting ART for adolescents and young adults in Kenya. EClinicalMedicine 2020; 25: 100453.