Two-drug regimens for the treatment of HIV in Africa

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Summary

Two-drug regimens (2DR) for the treatment of HIV are increasingly available. The oral regimen of dolutegravir and lamivudine is recommended as a preferred option in multiple national guidelines but is not currently included in WHO HIV treatment guidelines nor widely used in Africa. Long-acting injectable cabotegravir and rilpivirine is being rolled out in USA, Europe, and Australia but use in sub-Saharan Africa is currently limited to clinical trials. Given increasing life expectancy, rising prevalence of non-communicable diseases, and resulting polypharmacy among people living with HIV, there are potential advantages to the use of 2DR in this setting, particularly in African women, adolescents and older adults. Here we review existing evidence and highlight the risks, benefits and key knowledge gaps for the use of 2DR in programmatic care settings in Africa. We suggest that dolutegravir/lamivudine can be safely used as a suppressed switch option in programme settings once chronic hepatitis B has been excluded. Those switched to 2DR should receive hepatitis B vaccination. More efficacy data is needed to support dolutegravir/lamivudine in the test and treat approach and long-acting cabotegravir and rilpivirine in the public health system in sub-Saharan Africa.

Introduction

The rollout of antiretroviral therapy (ART) is a triumph of global public health. In 2022 there were 29.8 million people accessing ART, including 21.2 million in sub-Saharan Africa.[1] As a result, population-level life expectancy has increased dramatically. With this, long-term ART-related toxicities, including renal and cardiovascular disease, osteoporosis and metabolic complications, become more relevant. The WHO recently raised concerns that life expectancy gains are now being offset by rising non-communicable diseases.[2] Reducing the lifetime risk of ART toxicity by minimising cumulative drug exposure is therefore increasingly important.

Currently, the WHO-recommended first-line treatment regimen is dolutegravir with tenofovir disoproxil fumarate and lamivudine or emtricitabine. Tenofovir disoproxil fumarate has well-established kidney and bone toxicity and capacity to monitor complications is limited in many settings. Minimising toxicity by expanding the use of tenofovir-free two-drug regimens (2DR) is a compelling option. In recent years the results of several clinical trials (Table 1) have driven dolutegravir/lamivudine to the top of treatment guidelines in Europe and the USA (Table 2).[3] Only three trials have enrolled people living with HIV (PLWH) in sub-Saharan Africa, thus there is a dearth of data from the region to inform WHO policy and national treatment guidelines. We are not aware of any trials or observational studies on dolutegravir/lamivudine in programme settings in Africa currently. Gibas *et al.* provided a thorough review of the evidence for the use of 2DR with a focus on high-income settings, but there are unique considerations for programmatic care settings that we consider here.[3]

Other 2DRs have also been extensively studied. Dolutegravir/rilpivirine has been found to be non-inferior to three drug regimens (3DR), but food requirements and high prevalence of non-nucleoside reverse transcriptase inhibitors (NNRTI) resistance limit its use in Africa.[4] Several protease-inhibitor (PI)-based 2DR have proven efficacy in treatment naïve and virally suppressed individuals (Table 1); however, given their toxicity profile, drug-drug interactions, and cost, PI-based 2DR is less appealing at scale but is a potentially useful option for individualised care. The injectable 2DR of long-acting (LA) cabotegravir/rilpivirine is efficacious, safe, and tolerable and is US Federal Drug Authority (FDA) and European Medicines Agency (EMA) approved.[3] However, <10% of participants in the three registrational trials were recruited from sub-Saharan Africa and data on the implementation of injectable 2DR in the public health approach are currently lacking.

Here we discuss the potential benefits, risks and evidence gaps relating to integrase strand transfer inhibitors (INSTI)-based 2DR in sub-Saharan African programme settings.

Possible benefits of 2DR in Africa

Minimising toxicity

Renal dysfunction is more commonly seen in African PLWH, particularly those >60 years.[5] WHO recommends against initiating tenofovir disoproxil fumarate where the estimated

glomerular filtration rate (eGFR) is <50mL/min/1.73m^2 and suggests switching to an alternative in those developing renal impairment. The availability of renal function monitoring varies,[2] meaning it may not be possible to detect and address deteriorating kidney function. Additionally, treatment of individuals with established kidney disease is complicated by the need to switch and/or dose-adjust ART, potentially increasing pill burden and impacting adherence. Availability of single tablet, tenofovir-sparing regimens would simplify care. Although lamivudine usually requires dose adjustment with eGFR <50ml/min/1.73m^2, standard doses are safely used in moderate renal impairment, with FDA approving dolutegravir/lamivudine use in eGFR ≥30ml/min/1.73m^2.[6]

Tenofovir disoproxil fumarate is known to reduce bone mineral density (BMD), and women living with HIV in South Africa have been shown to experience greater BMD loss compared to HIV-negative counterparts.[7] Given the limited availability of bone health assessments and treatments across the African continent, avoiding contributory agents could benefit long-term bone health and reduce fracture risk.

In cases of tenofovir toxicity, current guidelines advise the use of zidovudine, abacavir or, where available, tenofovir alafenamide.[2] However, these NRTIs have well-established side effects. Abacavir is associated with hypersensitivity reactions and cardiovascular risk.[3] Zidovudine can cause haematological abnormalities, myopathy, and lipodystrophies.[2] Although tenofovir alafenamide is generally safer from a renal and BMD perspective, there are concerns around weight gain, particularly in black women when used in combination with INSTIs.[8] As such, there is a need for regimens that do not include tenofovir (disoproxil or alafenamide), abacavir or zidovudine, for African women in particular.

Special populations – children, adolescents and older adults

Africa is home to 90% of all children and adolescents living with HIV.[9] It is estimated that these individuals will have 10-15 additional years of NRTI exposure compared to adults living with HIV, with significant consequent cumulative toxicity, particularly affecting BMD.[9] WHO guidelines recommend against using tenofovir disoproxil fumarate in children for this reason, though approve its use in adolescents. Other guidelines however, recommend against its use in those <25 years, prior to peak bone mass accrual.[10] Dolutegravir/lamivudine may therefore be of particular benefit in children and adolescents.

Injectable 2DR may be of further benefit to children and adolescents due to reductions in pill burden, treatment fatigue, stigma, and risk of disclosure.[9] LA cabotegravir/rilpivirine is currently FDA and EMA approved for adolescents, although efficacy and safety data are awaited from the ongoing Long-acting Treatment in Adolescents (LATA) trial in sub-Saharan Africa.[11]

Benefits may also be seen at the opposite end of the life course. The incidence of polypharmacy (simultaneous use of ≥5 medications) increases with age. Older individuals are more likely to experience complex polypharmacy and drug-drug interactions, typically with cardiovascular, gastro-intestinal, hormone replacement, and antiplatelet/anticoagulant medications.[12] Populations experiencing polypharmacy may benefit from a reduction in the number of antiretroviral agents.

Cost benefit

Dolutegravir/lamivudine was predicted to save $800 million over 5 years in the USA if initiated by half of treatment-naïve adults.[13] Generic formulations of dolutegravir/lamivudine are already available for ~$50 per patient/year, approaching the $45 per patient/year cost of generic tenofovir/lamivudine/dolutegravir.[14] Modelling studies are needed to fully understand the potential long-term cost-savings.

Widespread use of injectable cabotegravir/rilpivirine for all eligible PLWH would increase overall costs to programmes. However, using a cost-effectiveness threshold of $500 per disability-adjusted-life-year averted, a modelling study predicted that if targeted at individuals with suboptimal adherence to oral ART, injectable cabotegravir/rilpivirine will be cost-effective in sub-Saharan Africa if priced at $120 per person/year.[15] Costs of cold chain (for LA rilpivirine) were not accounted for in this analysis and may pose logistical and cost barriers in some settings.

Possible risks with 2DR in Africa

Risk of drug resistance

The risk of emergent INSTI resistance on 2DR is important as dolutegravir is critical in both first- and second-line treatment.[2] Emergent INSTI resistance compromises future treatment, often resulting in the need for PI-based therapy. Dolutegravir/lamivudine appears suitably robust to mitigate the risk of emergent resistance as confirmed in GEMINI 1 and 2 and observational studies.[3] However, only treatment-naïve individuals with HIV RNA <500,000 copies/ml and without baseline resistance to dolutegravir or lamivudine were eligible. The prevalence of NRTI resistance in sub-Saharan Africa ranges from 32.5-55.3%, largely attributed to M184V mutation.[16] Baseline HIV RNA quantification and resistance testing are not routinely available, and proviral DNA testing even less so. Thus, clinicians are seldom privy to genotypic information. Some have concerns about the safety of using dolutegravir/lamivudine in the absence of genotypic information. However, reassuring data from a switch study of dolutegravir/lamivudine in heavily treatment-experienced adults with prior virological failure and prior/current M184V/I,[17] suggest that dolutegravir/lamivudine is efficacious in the presence of M184V/I through to 96-weeks. A multi-centre observational European cohort also reports comparable viral rebound and blips in adults with and without the M184V mutation 3 years after suppressed switch to dolutegravir/lamivudine (6.7% versus 6.9% respectively).[18] Finally, a recent systematic review found that M184V had minimal impact on virological suppression after switching to dolutegravir/lamivudine.[19]

In summary, we consider suppressed switch to dolutegravir/lamivudine in the absence of baseline genotypic information to be acceptable as the benefits likely outweigh the risks. However, given the current dearth of efficacy data on dolutegravir/lamivudine in the test and treat approach in programme settings, it is currently safer to first achieve viral suppression prior to switching to dolutegravir/rilpivirine in those who's HIV resistance profile and viral load is unknown. The recent STAT study in the USA examined dolutegravir/lamivudine in treatment-naïve but performed baseline genotype and subsequently switched those with baseline M184V back to 3DR.[20] In the treatment-naïve D2ARLING study investigators remained blinded to the baseline resistance results and viral suppression (<50copies/ml) at week 24 was comparable between the dolutegravir/lamivudine and the 3DR arm (94.34%

versus 95.37%, difference -1.03%, 95% CI -7.89% to 5.82%, p=0.97).[21] This is encouraging early data for dolutegravir/lamivudine in programme-style test and treat conditions, longer-term follow-up data is needed to support policy around this approach.

With regard to LA ART, the prevalence of INSTI resistance is currently low at 0.1%,[22] though predicted to increase with cumulative INSTI exposure and introduction of LA cabotegravir pre-exposure prophylaxis.[23] LA cabotegravir and rilpivirine have half-lives of 6-12 and 13-28 weeks respectively and can be detected in plasma for a year after a single injection.[24] This long pharmacokinetic tail in the context of late/missed injections, could result in emergent resistance. Robust scheduling, reminder, and tracing procedures must be in place to maximise adherence to +/-7 days of the planned injection, posing a challenge for overstretched clinics. In addition, rates of NNRTI resistance across Africa exceed 10%,[22] potentially undermining the efficacy of rilpivirine containing regimens. Results of the Cabotegravir and Rilpivirine Efficacy and Safety (CARES, PACTR202104874490818) trial will provide more insight into the magnitude of this risk.[11]

Finally, monitoring for treatment failure using HIV RNA is performed annually in most countries, thus failure can go unrecognised for prolonged periods risking onwards transmission, evolution of resistance and immune suppression. Whilst such events are rare with INSTI-based 2DR they are events of high clinical consequence, usually requiring future PI-based therapy, so caution should be taken to minimise risk. HIV RNA >200 copies/ml must be acted upon promptly with adherence intervention and repeat testing.

Risk around hepatitis B

WHO estimate that ~2.7 million (7.6%) PLWH are also living with hepatitis B virus (HBV) and the majority (69%; 1.9 million) live in sub-Saharan Africa.[2] NRTIs (tenofovir, lamivudine, emtricitabine) are effective against HBV and are recommended therapies for HIV/HBV co-infection. Abrupt discontinuation of NRTIs is discouraged due to the risk of HBV reactivation and hepatitis flares.[2] Lamivudine monotherapy in HIV/HBV co-infection is discouraged due to emergent HBV lamivudine resistance.[25] Therefore, until chronic HBV has been excluded it is necessary to use tenofovir-containing 3DR for HIV.

Whilst it is clear that 2DR should not be used in people with chronic HBV, it is uncertain how to approach the 42-62% of individuals in Africa with prior exposure but without evidence of chronic infection (positive core antibody (anti-HBc) with negative hepatitis B surface antigen (HepBsAg)).[26] Unfortunately, such individuals have largely been excluded from clinical trials (Table 1), despite minimal risk of HBV reactivation. The Veterans Ageing Cohort Study recently reported data from 5954 PLWH with positive anti-HBc but without active HBV, who were switched to ART regimens without HBV activity. The primary outcome of HBV reactivation (incident HepBsAg or HBV-DNA positivity) occurred in 0.7% of individuals and in 0.3% of those who were virologically suppressed. Essentially, the risk of HBV reactivation following 2DR switch is negligible in those with well-controlled HIV. Therefore, once active HBV is excluded, switch to 2DR can be made. Median time to HBV reactivation was 292 days (IQR: 164-816 days), so HepBsAg could be repeated after 1-2 years to identify the rare cases of reactivation.[27]

Since 2001, WHO recommended routine childhood HBV vaccination and by 2015, 95% of WHO member countries had included HBV vaccine in the Essential Program on Immunisation,

so HIV/HBV co-infection should become less of a concern.[28] However, whilst HBV vaccination is part of many national guidelines for PLWH, access to vaccines is limited, leaving most adults at risk of acquiring HBV,[26] a risk mitigated by taking tenofovir-based ART. In sub-Saharan Africa it is essential to vaccinate those switching to 2DR.

Metabolic risk

2DR studies have increased awareness that tenofovir disoproxil fumarate is lipid and weight suppressive. Removal of tenofovir disoproxil fumarate was associated with worsening lipid profiles in TANGO,[3] of unknown clinical relevance. Lipids are unlikely to be monitored in programmatic care and statins are often paid out of pocket so consistent lipid management is challenging. The relative lipid impact of LA cabotegravir/rilpivirine is currently unclear.

Switching to a tenofovir alafenamide-containing 3DR in combination with dolutegravir also caused lipid and weight gain in Southern Africans, with those in the tenofovir alafenamide group gaining 6kg on average, compared to 3kg in the tenofovir disoproxil-containing group.[8] In a follow-up sub-study of participants who switched back to tenofovir disoproxil fumarate there was a statistically significant reduction in weight for women.[29] This furthers the theory that tenofovir disoproxil fumarate suppresses weight so whilst tenofovir alafenamide-containing regimens might be essential in renal dysfunction, the metabolic trade-off must be considered, and dolutegravir/lamivudine may be preferable.

Tuberculosis

Tuberculosis (TB) and HIV remain syndemic in sub-Saharan Africa with 461,000 incident cases of TB/HIV coinfection in 2022.[30] Treatment guidelines do not recommend using dolutegravir/lamivudine in people being treated for TB as there is no efficacy data during rifampicin co-administration. Rifampicin reduces dolutegravir exposure by 70% so twice daily dosing is currently recommended.[3] Further pharmacokinetic and efficacy data are needed with dolutegravir/lamivudine.

Rifampicin reduces oral cabotegravir and rilpivirine trough exposures by 59% and 89% respectively.[31] Pharmacokinetic modelling studies predict a similar effect on the LA cabotegravir/rilpivirine formulations, warranting a switch back to suitable oral ART promptly after initiation of rifampicin.[31]

Pregnancy

Over half of all PLWH in sub-Saharan Africa are individuals of reproductive potential.[1] 2DR are not recommended in pregnancy due to lack of efficacy data for pregnancy and breastfeeding.[3] Data on maternal virological outcomes, vertical transmission and breastmilk viral load are needed. LA cabotegravir/rilpivirine comes with additional concern due to unknown effects of cabotegravir on the developing foetus, although data from pregnancies conceived on LA cabotegravir are reassuring.[32]

Discussion

Here we summarise the potential benefits and risks of 2DR use in programmatic care settings in Africa. Whilst a public health approach is required, increasing ART choice and individualised care for those with comorbidities, and reducing ART-related toxicity and polypharmacy is essential. At the end of 2021 PEPFAR estimated that 22% of all PLWH receiving ART were >50 years old, which will continue to increase year on year.[33]

Dolutegravir/lamivudine has been shown to be highly efficacious, tolerable, affordable, and durable over ~3-years of follow-up. As a tenofovir disoproxil fumarate and abacavir-sparing regimen, it is particularly attractive for ageing people at risk of renal and cardiovascular disease. Given concerns around weight gain with tenofovir alafenamide in black African women, a particular role for dolutegravir/lamivudine exists in this group.

More efficacy data is needed on dolutegravir/lamivudine in a test and treat approach in the face of NRTI resistance before this regimen can be recommended in ART naïve individuals in programme settings. However, following suppressed switch to dolutegravir/lamivudine the risk of virological failure and emergent drug resistance in people with underlying NRTI resistance is comparable to 3DR. So, suppressed switch to dolutegravir/lamivudine in the programme context without genotypic information and with annual HIV RNA testing is acceptable once chronic hepatitis B has been excluded (i.e. negative HepBsAg on serology or point of care test). Individuals switched to 2DR must receive hepatitis B vaccination. We encourage policy makers at WHO and national level to include this approach in future treatment guidelines. Currently, women conceiving on dolutegravir/lamivudine would need to more frequent monitoring or switch back to 3DR until completion of breastfeeding.

Evidence from the continent is urgently needed to guide policy and improve equitable access to dolutegravir/lamivudine in sub-Saharan Africa. Key evidence gaps that must be addressed are described in Box 1. Modelling studies must quantify the long-term health and quality of life outcomes, as well as cost-effectiveness in programme settings. Secondly, randomised clinical trials and observational studies among those with established renal dysfunction, older PLWH, children, adolescents, pregnant and breastfeeding women and treatment naïve groups are needed, with outcomes including viral suppression, weight, lipids, BMD, renal parameters, patient reported outcome measures and cost effectiveness. Three ongoing trials of injectable cabotegravir/rilpivirine with exclusive recruitment in Africa will yield policy-relevant results for adolescents and adults in the next two years, and other studies on injectable 2DR in children and pregnancy are underway.[11]

Widening access to 2DR in sub-Saharan Africa requires investment in research, infrastructure, supply chain (including cold chain for LA rilpivirine) and training for patients and providers. Policymakers, researchers, funders, clinicians, and the community must now strive to increase equity in access to the best treatment options available, ensuring that regimens with the lowest toxicity profiles are available to support individualised care.

Box. 1 – Evidence gaps for 2DR implementation in sub-Saharan Africa

1. Lack of data in extremes of age (>70 yrs, <18 yrs)
2. Impact of switch to 2DR on weight gain and lipids in African PLWH
3. Impact of 2DR versus tenofovir disoproxil fumarate-based 3DR in preventing development of renal dysfunction
4. Safety and efficacy of 2DR in chronic kidney disease (eGFR <50 ml/min/1.73m^2) in settings with limited capacity for renal monitoring
5. Safety of switch to 2DR in those with prior hepatitis B exposure in Africa, particularly without evidence of natural or vaccine-mediated immunity
6. Safety and efficacy of 2DR in absence of baseline HIV drug resistance testing, particularly as a test and treat strategy
7. Safety and efficacy of 2DR in pregnancy and breastfeeding
8. Data around cost-effectiveness of dolutegravir/lamivudine in a variety of population settings
9. Real world observational data and implementation studies in the WHO Africa region

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CN, DSL, FVC, IM, LAO contributed to the conceptualisation, data curation and methodology. CN, DSL, EL, FVC, IM, LA wrote the original draft. CN, DSL, EL, ER, FVC, IM, LAO, NO, SS reviewed and edited the original draft. DSL, ER, FVC provided supervision for the paper.

References

1 UNAIDS. Factsheet: Global HIV statistics. 2023 https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf (accessed Feb 24, 2024).

2 World Health Organization. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. 2021 https://www.who.int/publications/i/item/9789240031593 (accessed Feb 24, 2024).

3 Gibas KM, Kelly SG, Arribas JR, *et al.* Two-drug regimens for HIV treatment. Lancet HIV. 2022; **9**: e868–83.

4 Moorhouse MA, Cohen K. The role of rilpivirine in Southern Africa. *South Afr J HIV Med* 2019; **20**. DOI:10.4102/sajhivmed.v20i1.825.

5 Penner J, Ombajo LA, Otieno D, *et al.* High rates of kidney impairment among older people (≥ 60 years) living with HIV on first-line antiretroviral therapy at screening for a clinical trial in Kenya. *PLoS One* 2023; **18**: e0285787.

6 U.S. Food & Drug Administration. Supplement Approval NDA 211994/S-10: Dovato. 2021 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/211994Orig1s010ltr.pdf (accessed Feb 24, 2024).

7 Madanhire T, Goedecke JH, Ward KA, *et al.* The Impact of Human Immunodeficiency Virus and Menopause on Bone Mineral Density: A Longitudinal Study of Urban-Dwelling South African Women. *J Bone Miner Res* 2023; **38**. DOI:10.1002/JBMR.4765.

8 Venter W, Bosch B, Sokhela S, *et al.* Final week 192 results from the ADVANCE trial: first-line TAF/FTC/DTG, TDF/FTC/DTG vs TDF/FTC/EFV - weight gain. In: 24th Intl AIDS Conference. 2022. https://www.natap.org/2022/IAC/IAC_34.htm (accessed June 29, 2023).

9 Thornhill JP, Cromarty B, Gaddie J, Mushunje S, Ferrand RA. Two-drug antiretroviral regimens for HIV. *BMJ* 2023; **382**: e071079.

10 Waters L, Cromarty B, Dunn D, *et al.* BHIVA guidelines on antiretroviral treatment for adults living with HIV-1. 2022 https://www.bhiva.org/file/63513a1745ea9/BHIVA-guidelines-on-antiretroviral-treatment-for-adults-living-with-HIV-1-2022.pdf (accessed Feb 24, 2024).

11 Norcross C, Ombajo LA, Kassim S, Garrett N, Cresswell F V., Ruzagira E. Long-acting antiretrovirals: research and implementation considerations in Africa. *Lancet HIV* 2023; **10**: e428–9.

12 Marzolini C, Back D, Weber R, *et al.* Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother* 2011; **66**: 2107–11.

13 Girouard MP, Sax PE, Parker RA, *et al.* The Cost-effectiveness and Budget Impact of 2-Drug Dolutegravir-Lamivudine Regimens for the Treatment of

HIV Infection in the United States. *Clinical Infectious Diseases* 2016; **62**: 784–91.

14 The Global Fund. Global Fund Agreements Substantially Reduce the Price of First-line HIV Treatment to Below US$45 a Year. 2023. https://www.theglobalfund.org/en/news/2023/2023-08-30-global-fund-agreements-substantially-reduce-price-first-line-hiv-treatment-below-usd45-a-year (accessed Feb 24, 2024).

15 Phillips AN, Bansi-Matharu L, Cambiano V, *et al.* The potential role of long-acting injectable cabotegravir–rilpivirine in the treatment of HIV in sub-Saharan Africa: a modelling analysis. *Lancet Glob Health* 2021; **9**: e620–7.

16 Ssemwanga D, Lihana RW, Ugoji C, *et al.* Update on HIV-1 Acquired and Transmitted Drug Resistance in Africa. *AIDS Rev* 2015; **17**: 3–20.

17 Blick G, Cerreta E, Mancini G, Cosenza A, Fang L. Prior M184V/I and multiple prior virological failures have no impact on the efficacy of switching HIV+ adults to DTG/3TC through 96Wks in SOLAR-3D. In: IAS 2023, the 12th IAS Conference on HIV Science. Brisbane, 2023.

18 Santoro MM, Armenia D, Teyssou E, *et al.* Virological efficacy of switch to DTG plus 3TC in a retrospective observational cohort of suppressed HIV-1 patients with or without past M184V: the LAMRES study. *J Glob Antimicrob Resist* 2022; **31**: 52–62.

19 Kabra M, Barber TJ, Allavena C, *et al.* Virologic Response to Dolutegravir + Lamivudine in People With Suppressed HIV-1 and Historical M184V/I: A Systematic Literature Review and Meta-analysis. *Open Forum Infect Dis* 2023; published online Nov 1. DOI:10.1093/ofid/ofad526.

20 Rolle CP, Berhe M, Singh T, *et al.* Dolutegravir/lamivudine as a first-line regimen in a test-and-treat setting for newly diagnosed people living with HIV. *AIDS* 2021; **35**: 1957–65.

21 Cordova E, Hernandez Rendon J, Mingrone V, *et al.* Efficacy of dolutegravir plus lamivudine in treatment-naive people living with HIV without baseline drug-resistance testing: week 24 results of the randomized D2ARLING study. In: 12th IAS Conference on HIV Science. Brisbane, 2023.

22 World Health Organisation. HIV Drug Resistance Report. 2021 https://iris.who.int/bitstream/handle/10665/349340/9789240038608-eng.pdf?sequence=1 (accessed Feb 24, 2024).

23 Smith J, Bansi-Matharu L, Cambiano V, *et al.* Predicted effects of the introduction of long-acting injectable cabotegravir pre-exposure prophylaxis in sub-Saharan Africa: a modelling study. *Lancet HIV* 2023; **10**: e254–65.

24 Hodge D, Back DJ, Gibbons S, Khoo SH, Marzolini C. Pharmacokinetics and Drug-Drug Interactions of Long-Acting Intramuscular Cabotegravir and Rilpivirine. *Clin Pharmacokinet* 2021; **60**: 835–53.

25 Stewart B, Jobarteh ML, Sarge-Njie R, *et al.* Emergence of HBV resistance to lamivudine (3TC) in HIV/HBV co-infected patients in the Gambia, West Africa. *BMC Res Notes* 2011; **4**: 1–6.

26 McNaughton AL, Lourenço J, Bester PA, *et al.* Hepatitis B virus seroepidemiology data for Africa: Modelling intervention strategies based on a systematic review and meta-analysis. *PLoS Med* 2020; **17**. DOI:10.1371/JOURNAL.PMED.1003068.
27 Denyer R, Tate J, Benator D, Lim J, Weintrob A. HBV Reactivation in Person with HIV with Positive Hepatitis B Core Antibody after Switching to Antiretroviral Therapy without Hepatitis B Activity. In: IDWeek 2023. Boston, 2023.
28 World Health Organization. Global Hepatitis Report. 2017 https://www.who.int/publications/i/item/9789241565455 (accessed June 20, 2023).
29 Bosch B, Akpomiemie G, Chandiwana N, *et al.* Weight and Metabolic Changes After Switching From Tenofovir Alafenamide/Emtricitabine (FTC)+Dolutegravir (DTG), Tenofovir Disoproxil Fumarate (TDF)/FTC + DTG, and TDF/FTC/Efavirenz to TDF/Lamivudine/DTG. *Clin Infect Dis* 2023; **76**. DOI:10.1093/CID/CIAC949.
30 World Health Organisation. Global tuberculosis report. 2023 https://iris.who.int/bitstream/handle/10665/373828/9789240083851-eng.pdf?sequence=1 (accessed Feb 24, 2024).
31 Rajoli RKR, Curley P, Chiong J, *et al.* Predicting Drug–Drug Interactions Between Rifampicin and Long-Acting Cabotegravir and Rilpivirine Using Physiologically Based Pharmacokinetic Modeling. *J Infect Dis* 2019; **219**: 1735.
32 Patel P, Ford SL, Baker M, *et al.* Pregnancy outcomes and pharmacokinetics in pregnant women living with HIV exposed to long-acting cabotegravir and rilpivirine in clinical trials. *HIV Med* 2023; **24**. DOI:10.1111/HIV.13439.
33 President's Emergency Plan for AIDS Relief. Report to Congress on PEPFAR Treatment Report 22 USC 7611(g): Development of a Comprehensive, Five-year, Global Strategy. 2022 https://www.state.gov/wp-content/uploads/2023/01/Tab-1-2022-PEPFAR-Annual-Treatment-Report.Dec-2022-1.pdf (accessed Feb 24, 2024).