Use of integrase inhibitors in HIV-associated tuberculosis in high-burden settings: implementation challenges and research gaps

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People living with HIV have a higher risk of developing tuberculosis, and tuberculosis is one of the leading causes of death among people living with HIV globally. Treating HIV and tuberculosis concurrently has morbidity and mortality benefits. However, HIV and tuberculosis co-treatment is challenging due to drug–drug interactions, overlapping toxicities, tuberculosis-associated immune reconstitution syndrome, and concerns for treatment failure or drug resistance. Drug–drug interactions between antiretrovirals and tuberculosis drugs are driven mainly by the rifamycins (for example, the first-line tuberculosis drug rifampicin), and dose adjustments or drug switches during co-treatment are commonly required. Several implementation challenges and research gaps exist when combining the integrase strand transfer inhibitors (INSTIs), highly potent antiretroviral drugs recommended as first-line treatment of HIV, and drugs used for the treatment and prevention of tuberculosis. Ongoing and planned studies will address some critical questions on the use of INSTIs in settings with a high tuberculosis burden, including dosing of dolutegravir, bictegravir, and cabotegravir when used with the rifamycins for both tuberculosis treatment and prevention. Failure, in the past, to include people with tuberculosis in HIV clinical treatment trials has been responsible for some of the research gaps still evident for informing optimisation of HIV and tuberculosis co-treatment.

Introduction

Second-generation integrase strand transfer inhibitors (INSTIs) have high antiviral potency, favourable safety and tolerability profiles, and a high barrier to the development of HIV-1 resistance. Further, many INSTIs are available as single tablet fixed-dose combinations, suitable for once-daily administration.[1,2] For years, the USA and Europe have recommended INSTI-based treatment as preferred regimens for the treatment of HIV.[3] In 2018, WHO, for the first time, recommended an INSTI-based regimen—namely dolutegravir plus two nucleoside reverse transcriptase inhibitors—as first-line therapy for the treatment of HIV-1 infection in adults, adolescents, and children in low-income and middle-income countries and regions, such as southern and eastern Africa, where pre-treatment drug resistance to the non-nucleoside reverse transcriptase inhibitors reaches 10%.[4,5] In many settings where HIV prevalence is high, tuberculosis is common and must be treated alongside HIV. Many research and implementation gaps remain for the successful use of INSTIs among people with HIV-associated tuberculosis in high-burden settings.

Status of INSTI use in low-income and middle-income countries

Approximately 40 million people live with HIV worldwide, and about half of them live in eastern and southern Africa. By the end of 2019, an estimated 25 million people were accessing antiretroviral therapy (ART) globally.[6] By mid-2020, about 100 low-income and middle-income countries had adopted or were planning to incorporate dolutegravir into their national treatment guidelines, including countries in sub-Saharan Africa.[7] INSTIs have the potential to change the outcomes of HIV treatment programmes, given their improved tolerability profile, high barrier to drug resistance, availability of cost-effective single tablet co-formulations, and robustness in settings where stockouts might occur with the need to stop and restart drug regimens.[5,8] Data from a retrospective cohort study in Botswana suggest better tuberculosis treatment outcomes in people on dolutegravir-based versus non-dolutegravir-based regimens; however, this needs further investigation.[9] In the INSPIRING study, tuberculosis treatment success rates were high in both the efavirenz (91%) and dolutegravir (88%) groups, with no tuberculosis treatment failures in the dolutegravir group.[10] Despite emerging findings from studies in sub-Saharan Africa related to weight gain and previous concerns for congenital anomalies,[11,12] recent modelling studies found that a policy of ART initiation with a dolutegravir-based regimen in low-income and middle-income countries, including in women intending pregnancy, was predicted to bring net population health benefits and to be cost-saving.[13] Although dolutegravir is increasingly available, usually in combination with tenofovir disoproxyl fumarate and lamivudine, other INSTIs (table) are not readily available in most low-income and middle-income countries. The first-generation INSTIs, raltegravir and cobicistat-boosted elvitegravir, are not part of the recommended first-line or second-line drug regimens in adults, adolescents, or children in low-income and middle-income countries. Bictegravir (marketed in a single tablet combination pill with tenofovir alafenamide and emtricitabine, as Biktarvy) is among the most heavily prescribed ART regimens in the USA, but it is not yet registered in African settings. Cabotegravir, given via oral lead-in and then as a long-acting injectable together with rilpivirine, shows promise for both HIV treatment and prevention. For most

	Regimens or formulations	Metabolism	Can the INSTI be co-administered with a rifamycin?		
			Rifampicin	Rifabutin	Rifapentine
First-generation INSTIs					
Raltegravir	Raltegravir 400 mg (Isentress) plus two NRTIs.	UGT1A1	Yes. Decreases plasma concentrations of raltegravir; double raltegravir dose to 800 mg twice daily[14,15] and double weight-based dose in children >4 weeks old.[16,17]	Yes. No dose adjustment; use 400 mg twice daily (standard dose).[18]	Yes. No dose adjustment with rifapentine 1200 mg weekly with isoniazid for tuberculosis prevention; studies needed for daily rifapentine dosing during tuberculosis treatment.[19]
Elvitegravir	Stribild (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir disoproxil fumarate 245 mg); Genvoya (elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg).	UGT1A1, CYP3A4	No.* Do not co-administer.	No.* Do not co-administer.	No.* Do not co-administer.
Second-generation INSTIs					
Dolutegravir	TLD (dolutegravir 50 mg, lamivudine 300 mg, and tenofovir 300 mg); Triumeq (dolutegravir 50 mg, abacavir 300 mg, and lamivudine 300 mg); Tivicay (dolutegravir 50 mg) plus one or two NRTIs.	UGT1A1, CYP3A4	Yes. Decreases plasma concentrations of dolutegravir; double recommended dolutegravir dose to 50 mg twice daily—eg, TLD plus dolutegravir single 50 mg tablet given as evening dose for adults, adolescents, and children >30 kg†[10,20,21] There is evidence for double dose in children >6 years old.[20]	Yes. No dose adjustment needed.[17]	Yes. No dose adjustment with rifapentine 1200 mg weekly with isoniazid for tuberculosis prevention; studies are needed for daily rifapentine dosing during tuberculosis treatment.[16] There is an ongoing study (NCT04272242) investigating rifapentine used daily for 1 month with dolutegravir.
Bictegravir	Biktarvy (bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg).	UGT1A1, CYP3A4, P-glycoprotein	No.‡ Strongly decreases plasma concentrations of bictegravir. A study found a 60% decrease in AUC and 80% decrease in trough concentrations in HIV-negative volunteers; not yet studied in patients with HIV and tuberculosis co-infection on rifampicin-based tuberculosis treatment.[22]	No.‡ Decreases plasma concentrations of bictegravir; 38% and 56% decrease in AUC and trough concentrations. No clinical data to suggest that this interaction is clinically acceptable in patients with HIV and tuberculosis.[18]	No.* No data.
Third-generation INSTIs					
Cabotegravir	Cabotegravir oral tablets 30 mg; cabotegravir injectable Cabenuva (long-acting injectable cabotegravir 200 mg/mL plus rilpivirine 300 mg/mL).	UGT1A1 (main), CYP3A4 to a lesser extent, P-glycoprotein	No.‡ Decreases plasma concentrations of cabotegravir; 59% decrease in AUC shown with cabotegravir 30 mg oral tablet. Rilpivirine exposure can also be reduced by rifampicin.[23]	No.‡ Decreases plasma concentrations of cabotegravir; data from healthy volunteer study found a 27% increase in clearance with cabotegravir 30 mg tablet, suggesting a relatively low reduction in drug exposure; however, this needs to be studied in patients with HIV and tuberculosis co-infection and utilising the intramuscular formulation.[24]	No.* No data.

AUC=area under the curve. INSTI=integrase strand transfer inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. *Not studied. †>35 kg based on South African guideline. ‡Based on data from healthy volunteer studies.

Table: **Considerations for INSTI and rifamycin co-administration**

countries, having a first-line ART regimen that can be used widely, in all populations, including pregnant women, children, and people with HIV-associated tuberculosis, is highly desirable. Thus, incompatibility with tuberculosis treatment is a barrier to introduction of HIV medicines globally.

HIV-associated tuberculosis: the magnitude of the problem and co-treatment challenges

Of 10 million incident cases of tuberculosis globally in 2019, roughly 9% had HIV.[25] Among people living with HIV, tuberculosis disease is the leading cause of death. WHO identified 30 countries with the highest burden of HIV–tuberculosis co-infection rates, with approximately 23 of these in sub-Saharan Africa.[26] Current standard of care is to treat HIV and tuberculosis concurrently, as there is a morbidity and mortality benefit of doing so, especially for people with low CD4 cell counts.[12,13] Co-treatment of HIV and tuberculosis, although ideal, has its challenges, mainly driven by drug–drug interactions with the rifamycins. Rifampicin is a critical component of standard first-line tuberculosis drug regimens because of its unique sterilising activity.[13] However, rifampicin is a potent inducer of cytochrome P450 (CYP) enzymes, the UDP-glucuronosyltransferases (UGTs), and drug transporters such as P-glycoprotein (also known as MDR1), and therefore causes several clinically significant drug–drug interactions, including with INSTIs.[27] Rifabutin, a less

potent inducer of drug-metabolising enzymes (UGT and CYP34A) and transporter enzymes (P-glycoprotein), has a lesser effect on INSTI exposure than rifampicin. Rifabutin might be an alternative to rifampicin for treatment of tuberculosis in settings where it is available.[18] Pharmacokinetic data from HIV-negative participants in drug interaction trials suggest rifabutin can be used with INSTIs without dose adjustments. However, there are no randomised controlled trials comparing treatment outcomes in people with HIV-associated tuberculosis receiving rifampicin versus rifabutin. Additionally, limited efficacy and safety data exist for rifabutin use in children.[18,28] WHO recommends rifapentine for tuberculosis prevention in combination with isoniazid, weekly over 3 months,[29] and rifapentine is now registered for use in children aged 2 years or older for tuberculosis prevention. For tuberculosis treatment, a 4-month rifapentine-containing regimen was recently found to be non-inferior to the 6-month first-line standard of care for treatment of drug-susceptible tuberculosis, when used as part of a regimen containing isoniazid, moxifloxacin, and pyrazinamide.[30] WHO now recommends this 4-month regimen as an alternative therapy for drug-sensitive tuberculosis.[31] Rifapentine, however, like rifampicin, is a potent inducer of metabolising enzymes.[32] Currently, rifabutin and rifapentine are not readily available in most low-income and middle-income countries, as cost is prohibitive, and these drugs are not available as part of fixed-dose combinations for ease of use. Nevertheless, efforts are underway for affordable global access to rifapentine for tuberculosis prevention through partners such as Unitaid, Sanofi, and the Global Fund to Fight AIDS, Tuberculosis and Malaria. With regard to drug-resistant tuberculosis, based on knowledge of metabolic pathways, despite potential for interactions,[33] there appears to be a low likelihood of clinically meaningful drug interactions between INSTIs and second-line tuberculosis drugs including the fluoroquinolones, bedaquiline, linezolid, and clofazimine, and newer drugs such as pretomanid. In the ZeNix study,[34] pretomanid was used with bedaquiline and linezolid (BPaL regimen) and most people with HIV in the study were treated with dolutegravir-based ART, with no concerns. Overlapping toxicities (eg, hepatotoxicity, central nervous system side effects) are a theoretical concern, but there are limited clinical data from people with multidrug-resistant tuberculosis taking INSTI-containing regimens with which to assess drug interaction or safety risks.[33,35]

Opportunistic infections are common in people with HIV-associated tuberculosis, particularly in sub-Saharan Africa. Therefore, clinicians need to be aware of and monitor for drug interactions between HIV and tuberculosis drug regimens, including potential interactions with commonly prescribed antifungal, antimalarial, antiviral, and other drugs used for treatment of opportunistic infections. Other comorbid conditions such as tuberculosis-related transient hyperglycaemia[36] should also be considered, with additional monitoring for these, given findings published in recent case reports of dolutegravir-related new-onset or worsening hyperglycaemia.[37]

Tuberculosis and HIV co-treatment for adults and children

Dolutegravir

Rifampicin induces UGT1A1 and CYP3A4 enzymes, which increases dolutegravir metabolism and decreases drug concentrations (table).[38] Increasing the dose of dolutegravir from 50 mg once daily to 50 mg twice daily was shown to be effective at 48 weeks in HIV treatment-naive adults with tuberculosis in the INSPIRING study.[10] Based on this study, WHO recommends twice-daily dolutegravir 50 mg dosing for HIV-1 infection during co-treatment with rifampicin for tuberculosis.[39] Dolutegravir dosing, using 50 mg film-coated tablets, has recently been established for children weighing 20 kg or more.[40,41]

Although the drug interaction between dolutegravir and rifampicin-based tuberculosis treatment in adults is well characterised, and dosing to mitigate it is established, twice-daily dosing (with a fixed-dose combination in the morning and stand-alone dolutegravir in the evening using a single dolutegravir tablet) is challenging in programmatic settings. Firstly, adherence to treatment can be affected by (1) the need for twice-daily versus once-daily dosing with fixed-dose combination single tablet formulations; (2) higher pill burden with tuberculosis and HIV drug co-treatment; and (3) overlapping toxicities with tuberculosis and HIV drugs. Secondly, potential for stockouts, which are common in resource-limited settings (particularly for single drugs such as dolutegravir 50 mg, used for adjusted dosing), might result in the need to switch people to non-dolutegravir-based regimens during rifampicin co-treatment. Thirdly, if tuberculosis and HIV clinic staff do not communicate well, people might not be initiated on or switched to a dolutegravir twice-daily regimen during rifampicin co-treatment. A retrospective cohort study from Botswana reported that around 44% of people on dolutegravir during rifampicin-based tuberculosis treatment were on once-daily dolutegravir, deviating from the national guideline to dose dolutegravir twice daily during tuberculosis treatment with rifampicin.[9] Furthermore, people who are initiated on the twice-daily dolutegravir regimen might not be promptly switched back to once-daily dosing after tuberculosis treatment completion. While this might result in substantial toxicities for other antiretroviral drugs (eg, double-dose boosted protease inhibitors continued after rifampicin-based tuberculosis treatment is stopped), twice-daily dolutegravir is typically well tolerated, without concerns of potentiated overlapping toxicities with twice-daily versus once-daily dosing, and is standard of care for some people with resistance to certain INSTIs, without additional monitoring required. Despite these challenges, favourable

HIV and tuberculosis treatment outcomes observed within the Botswana programmatic roll-out among people with HIV and tuberculosis co-infection using dolutegravir-based regimens have been encouraging.[9]

No dose adjustment is required for dolutegravir when co-administered with once-weekly rifapentine plus isoniazid for tuberculosis prevention. Nor is a dose adjustment required when dolutegravir is given together with rifabutin for tuberculosis treatment.[16]

Several key questions remain. First, can dolutegravir be dosed once daily with rifampicin? Some evidence supports once-daily dolutegravir dosing during rifampicin co-treatment. A drug–drug interaction study in healthy volunteers showed that although dolutegravir given once daily at 50 mg or 100 mg produced plasma concentrations that were considerably reduced by co-administration with rifampicin, the concentrations were still above the protein-binding-adjusted IC_{90} (drug concentration required to inhibit 90% of in-vitro viral replication) of 64 ng/mL, suggesting adequate exposure for efficacy.[42] A randomised controlled trial (RADIANT) is underway in South Africa to determine the efficacy of once-daily dolutegravir 50 mg during tuberculosis treatment with rifampicin in ART-naive adults with HIV-1 infection (NCT03851588). The results of the RADIANT study are anticipated in 2022. Evidence from a retrospective cohort study in a programmatic setting in Botswana showed similar high viral suppression rates in the 44% of people who were given dolutegravir once daily compared with twice daily during co-treatment with rifampicin for tuberculosis, which supports once-daily dolutegravir dosing; although these data are supportive, they should be interpreted cautiously given the retrospective study design.[9] Second, in the subset of people who are on effective ART with viral suppression who develop drug-susceptible tuberculosis, might once-daily dolutegravir be adequate for maintaining virological suppression during rifampicin co-treatment? This needs to be investigated prospectively. Third, what are the appropriate doses of dolutegravir to use in children, particularly young children, taking rifampicin-based tuberculosis treatment? Limited data exist for dolutegravir dosing in children with HIV-associated tuberculosis, but WHO nevertheless recommends the use of dolutegravir 50 mg dosed twice daily in children weighing at least 20 kg while on rifampicin-based treatment.[43] In the 13 children age 6–18 years who developed tuberculosis while on dolutegravir-based ART (50 mg or 25 mg) in the ODYSSEY study and were transitioned to twice-daily dosing, the treatment was safe and effective.[20] No published data with rifampicin exist for younger children, although studies are underway.[44] WHO endorses the use of dolutegravir, including twice-daily dosing in infants older than 4 weeks or weighing more than 3 kg,[21] noting the need for evidence to support this, as well as for treatment options in children younger than 4 weeks or weighing less than 3 kg with or without tuberculosis. Finally, studies are needed for daily rifapentine dosing during tuberculosis treatment with dolutegravir in adults and during weekly dosing for tuberculosis prevention in children younger than 2 years.[16]

Bictegravir

Bictegravir is metabolised predominantly by CYP3A and UGT1A1 (table). In a study involving HIV-negative healthy volunteers, bictegravir concentrations, when bictegravir was given twice daily with standard-dose rifampicin versus once daily alone, were reduced from 3070 µg/mL to 608 µg/mL (80% reduction), and the area under the plasma concentration–time curve for the 24 h post-dose period (AUC_{0-24}) was reduced on average by approximately 60%.[22] Trough concentrations of INSTIs including bictegravir have been shown to be strongly associated with antiviral activity. The protein-adjusted 95% effective trough concentration (EC_{95}) of bictegravir is approximately 162 ng/mL. In phase 3 efficacy studies of bictegravir at a dose of 50 mg once daily, bictegravir trough concentrations were found to be 16 times higher than the protein-adjusted EC_{95}. Despite the 80% reduction in bictegravir trough concentration with rifampicin co-administration, average trough concentration remained 3·1-fold higher than the protein-adjusted EC_{95}, and all participants in the healthy volunteer study maintained trough concentrations higher than the protein-adjusted $EC_{95.}$ However, a modelling exercise using data from phase 3 trials suggested that in a larger population of people, giving bictegravir twice daily with rifampicin can result, uncommonly (about three in 1000), in trough concentrations lower than the protein-adjusted EC_{95}.[22] Although the tenofovir disoproxil fumarate formulation of tenofovir can be used without dose adjustment with tuberculosis drugs, for tenofovir alafenamide, there has been concern that it might not achieve target concentrations when given with rifampicin, because it is a P-glycoprotein substrate. Tenofovir alafenamide undergoes phosphorylation to form the active moiety tenofovir diphosphate within lymphoid cells, where it also exerts its activity.[18,27] In a trial among healthy HIV-negative volunteers, tenofovir alafenamide, when dosed together with rifampicin 600 mg, produced intracellular tenofovir diphosphate concentrations that were over 82% higher on average than those achieved by standard-dose tenofovir. These data support further study of tenofovir alafenamide when co-administered with rifampicin in people with HIV and tuberculosis.[30] In the same study, rifampicin did not affect emtricitabine pharmacokinetics. Currently, there is no recommendation for the use of bictegravir among people with HIV who have tuberculosis. This represents a barrier to the introduction of this drug in sub-Saharan Africa and other high-burden settings.

Can bictegravir, tenofovir alafenamide, and emtricitabine in combination (Biktarvy) be taken twice daily together with rifampicin-containing tuberculosis

therapy among people with HIV-associated tuberculosis? What is the clinical relevance of the aforementioned drug interactions among people taking bictegravir, tenofovir alafenamide, and emtricitabine twice-daily combination HIV treatment receiving full first-line tuberculosis treatment (isoniazid, rifampicin, pyrazinamide, and ethambutol)? In the initial phase 1b trial of bictegravir monotherapy in which the drug was given at doses of 5, 25, 50, or 100 mg daily for 10 days to HIV treatment-naive people (mean baseline HIV viral load of 4·4 log), even the 5 mg dose was potent, reducing viral load substantially (1·5 log in 10 days), without emergence of resistance after stopping the drug.[8] Subsequent phase 2 and 3 trials of combination therapy evaluated the drug at 75 mg (phase 2) or 50 mg (phase 3).[29] At those doses, no pharmacokinetic–pharmacodynamic relationships could be seen, and no resistance emerged. Moreover, bictegravir has a long (38 h) dissociation half-life from the integrase enzyme, which will likely mitigate against potential breakthrough viraemia in the small minority of participants who might theoretically have trough concentrations below the protein-adjusted EC_{95} on rifampicin.[45] Bictegravir is not available as a single 50 mg tablet formulation. The pharmacokinetic profile of tenofovir alafenamide and emtricitabine when dosed twice daily with isoniazid, rifampicin, pyrazinamide, and ethambutol, and the safety and efficacy of these drugs as part of combination therapy in people with HIV-associated tuberculosis, is untested. Emtricitabine, however, is a well-tolerated drug, even at higher dosing levels (300 mg once daily[30] or 200 mg twice daily).[31] Among people with moderate renal impairment receiving the standard 200 mg dose, increases in emtricitabine exposure did not have an impact on safety.[32] Fixed-dose combination elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (Genvoya) full-strength tablets have been given to children as light as 25 kg, resulting in high mg/kg doses and exposures of emtricitabine and tenofovir alafenamide that were 75% and 71% higher, respectively, than average in adults, yet all participants tolerated the regimen well; there were no serious adverse events or adverse event-related discontinuations.[33] In a study of adults with HIV and end-stage renal disease, standard-dose elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide produced elevated drug concentrations, but the overall safety profile was not affected.[34] Moreover, because emtricitabine is renally eliminated and its exposures had previously been observed to be increased in adults with mild-to-moderate renal impairment, analysis of adverse events potentially associated with emtricitabine (ie, among those listed in the prescribing information as having at least 10% incidence), was carried out separately in the study. The overall incidence of these prespecified events occurred in nearly half of study participants; however, those events considered to be related to the study drug were reported for less than 10%, all were grade 1 or 2 in severity, and none led to premature discontinuation of study drug.[34] In the healthy volunteer study of bictegravir, tenofovir alafenamide, and emtricitabine twice daily with rifampicin, emtricitabine concentrations were, not surprisingly, doubled; no additional safety concerns were reported, although long-term data will be needed.[22]

If co-formulated bictegravir, tenofovir alafenamide, and emtricitabine given twice daily is safe and effective in people with HIV-associated tuberculosis, this will be an important option. As it is easier for programmes in low-income and middle-income countries to deliver similar formulations of drugs for different populations (rather than different drugs for people with and without tuberculosis), this will also be a helpful missing piece for the introduction of bictegravir, tenofovir alafenamide, and emtricitabine fixed-dose combination, highly popular in the USA and Europe, to Africa. Additionally, it will be helpful for tenofovir alafenamide roll-out. Tenofovir alafenamide has a better safety profile for bone and renal adverse events than tenofovir, but its introduction in many settings has been hindered, in part, by absence of data in people with HIV–tuberculosis co-infection. A trial of twice-daily bictegravir, tenofovir alafenamide, and emtricitabine together with first-line tuberculosis treatment is underway (NCT04734652).

Rifabutin reduces bictegravir exposure less than rifampicin in healthy volunteers, and clinical data in people with HIV–tuberculosis co-infection is needed to determine the clinical relevance of this interaction.[18] No data is available from interaction studies with rifapentine, although studies in healthy volunteers are currently underway (NCT04551573).

Other INSTIs

A study in people with HIV–tuberculosis co-infection suggested that doubling the dose of raltegravir to 800 mg twice daily overcompensated for rifampicin induction, and that a standard raltegravir dose with rifampicin resulting in a modest (31%) decrease in trough concentration of raltegravir would be sufficient.[14] However, non-inferiority after 48 weeks of treatment could not be statistically demonstrated for raltegravir 400 mg twice daily compared with efavirenz 600 mg daily in a phase 3 trial in adults with HIV-associated tuberculosis using rifampicin-based tuberculosis treatment simultaneously. While virological suppression was similar over the course of tuberculosis treatment (first 24 weeks) in the two groups and virological non-suppression appeared to occur later in treatment (suggesting that twice-daily dosing of raltegravir rather than drug interactions was the underlying reason for failing to meet non-inferiority margins), the 400 mg twice-daily dose is nonetheless not recommended as first-line therapy for treatment of HIV (table).[46,47] WHO recommends raltegravir 800 mg twice daily with rifampicin as an alternative option in adults in settings where the drug is available, and raltegravir dose (weight-based dosing) can be doubled in children older

than 4 weeks when co-administered with rifampicin.[16,17] No dose adjustment is needed when raltegravir is co-administered with rifabutin or with rifapentine when given once weekly for tuberculosis prevention;[48] however, no data are available for co-treatment with rifapentine dosed daily. Elvitegravir is an alternative INSTI option; however, it is not readily available in low-income and middle-income countries and requires boosting with cobicistat. Elvitegravir is not recommended for co-administration with rifampicin, rifabutin, or rifapentine. Cabotegravir long-acting injectable, given 2 months apart, has recently been shown to be superior to tenofovir disoproxil fumarate plus emtricitabine for the prevention of HIV infection, based on data from the HPTN 077 trial.[49] Cabotegravir, co-formulated with rilpivirine as a long-acting injectable, has been shown to be safe and effective for the treatment of HIV when given monthly,[24] and has been approved by the US Food and Drug Administration. Data from healthy volunteers suggest that cabotegravir can be used with rifabutin without dose adjustment,[23,50] but studies in people with HIV and tuberculosis will need to confirm this. Cabotegravir is not currently recommended to be co-administered with rifampicin or rifapentine. Whether or not altering the dosing frequency will mitigate drug interactions with cabotegravir (and rilpivirine) requires further study.[51,52]

Tuberculosis-associated immune reconstitution inflammatory syndrome and INSTIs

A well-known risk factor for development of immune reconstitution inflammatory syndrome (IRIS) is rapid decline in HIV-1 viral load. Initially there was a theoretical concern that INSTIs, which are quite potent and reduce viral load more rapidly than many other classes of antiretroviral drugs, would confer an unacceptably high risk of IRIS. In observational cohort studies, INSTIs have been associated with higher risks of IRIS.[15,53] However, in randomised controlled trials, this effect has not been confirmed.[10,54] Early ART initiation (within 1–4 weeks) is associated with increased risk of IRIS in people with low CD4 cell counts generally.[11,12] A systematic review did not report rapid decline in viral loads to be consistently associated with an increased risk of tuberculosis-associated IRIS.[55] Dolutegravir and raltegravir have been reported to improve immune recovery and might reduce the incidence of immune–virological discordance, which is seen in HIV-associated tuberculosis, particularly in people with advanced immunosuppression.[10,56,57]

The risk of IRIS in people with advanced AIDS (CD4 count <50 cells per μL), a population commonly started on ART soon after initiating tuberculosis treatment, is especially high, but this population was not studied in the INSPIRING or REALITY trials.[10,54] Further studies are necessary to evaluate whether dolutegravir increases the risk of tuberculosis-associated IRIS, particularly in people with advanced AIDS, and whether that population would benefit from closer monitoring or empirical steroids for IRIS prophylaxis.[58] Bictegravir has not been studied in people with HIV and tuberculosis co-infection.

***Panel*: Key research gaps and questions to be addressed in the use of INSTIs in HIV-associated tuberculosis**

- Is dolutegravir once-daily dosing during rifampicin co-treatment adequate and effective?
- What doses of dolutegravir should be used in children, including young children and those weighing >3 kg and <20 kg, taking rifampicin-based tuberculosis treatment?
- What about treatment options for neonates <4 weeks of age and <3 kg? Can weight-based dolutegravir be used in this group and what is the optimal dose in those taking rifampicin-based tuberculosis treatment?
- Is dolutegravir once-daily dosing safe and effective during rifapentine co-treatment when dosed daily for the treatment of tuberculosis and in children for tuberculosis treatment or prevention?
- In people who are on effective antiretroviral therapy and virally suppressed who develop drug-susceptible tuberculosis, is once-daily dolutegravir dosing adequate during rifampicin co-treatment to maintain virological suppression?
- Are there any clinically relevant drug–drug interactions between dolutegravir and combination drug regimens used in the treatment of drug-resistant tuberculosis?
- Is twice-daily bictegravir, tenofovir alafenamide, and emtricitabine safe and effective for the treatment of HIV in people receiving rifampicin-containing tuberculosis treatment?
- Can bictegravir, tenofovir alafenamide, and emtricitabine be dosed once daily (standard dose) for treatment of HIV when rifabutin is used as an alternative rifamycin? Is once-daily or twice-daily bictegravir dosing adequate when it is given with rifapentine weekly (for prevention) or daily (for prevention or treatment)?
- Can cabotegravir and rilpivirine long-acting injectables be safely dosed with the rifamycins with or without dose adjustment?
- What are the toxicity risks when INSTIs and tuberculosis drugs are given during programmatic roll-out and implementation (particularly when INSTI doses are adjusted or increased during tuberculosis co-treatment), with focus on hepatotoxicity, neuropsychiatric adverse events, and weight gain?
- Is the risk of immune reconstitution inflammatory syndrome different for INSTI-based treatment versus other antiretroviral drugs among people with low CD4 cell counts and advanced HIV disease?

INSTI=integrase strand transfer inhibitor.

Adverse events and overlapping toxicities in the context of HIV-associated tuberculosis

People with HIV–tuberculosis co-infection can be at higher risk for INSTI-associated adverse events, including neuropsychiatric adverse events, hepatic or renal toxicities, or weight gain, due to overlapping toxicities with tuberculosis drugs or higher drug exposure due to dose adjustments.[59] In early phase 2 and 3 dolutegravir safety and efficacy clinical trials, adverse events related to dolutegravir-containing ART regimens have been reported to be low, and the drug is better tolerated than efavirenz or protease inhibitor-containing ART. Safety data from these studies are primarily in the context of resourced settings in White, male (roughly 80%) participants[57,60,61] Limited data are available in resource-limited and programmatic settings where the majority of people are Black, African, and female, or in the context of co-treatment with tuberculosis drugs which can result in potentiated or

overlapping toxicities. Some retrospective safety data from programmatic roll-out in Botswana are reassuring.[9] However, with the expanded use of dolutegravir in ART treatment programmes in other African settings, monitoring of adverse events and treatment discontinuations in the context of diverse populations and high burden of HIV-associated tuberculosis, particularly related to emerging reports of neuropsychiatric adverse events, is needed. Further exploration is required to establish whether or not twice-daily dolutegravir dosing with rifampicin, potentially resulting in higher maximum concentrations of dolutegravir, could result in higher incidence of adverse events such as weight gain and neuropsychiatric adverse events (potentiated by isoniazid-associated neuropsychiatric adverse events including psychosis, particularly in people with slow acetylator status) or increased risk of congenital abnormalities.[62] It is also worth noting that WHO recommends dolutegravir in women of childbearing potential, since incidence of dolutegravir-associated neural tube defects was found to be lower than previously reported; close monitoring and informed decisions by women in consultation with health-care providers is warranted.[63]

Conclusions

Co-treating HIV and tuberculosis remains a challenge, and increased vigilance is required to manage dose adjustments and monitoring of toxicities and tuberculosis-associated IRIS. WHO has endorsed efforts to harmonise first-line ART using dolutegravir-based regimens across regions and age groups; however, implementation remains a challenge. A number of research gaps exist when combining the INSTIs and drugs used for the treatment and prevention of tuberculosis, which need to be addressed (panel). Ongoing and planned studies will address critical questions on INSTI use in settings with a high burden of tuberculosis, including dosing of dolutegravir, bictegravir, and cabotegravir when used with the rifamycins for both tuberculosis treatment and prevention. Failure, in the past, to include people with tuberculosis in HIV clinical treatment trials has been responsible for some of the research gaps still evident for informing optimisation of HIV and tuberculosis co-treatment. It is important going forward for any planned studies of new antiretroviral drug formulations, including the INSTIs, to be designed to include people with tuberculosis, especially studies in high-burden settings.

Contributors

AN conceptualised the Viewpoint and wrote the original draft. KED, KN, and NP reviewed and edited the Viewpoint. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

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