Two-drug antiretroviral Therapy for HIV

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Clinical Case

Mr Smith is a 59-year-old man who has been living with HIV for 15 years. He has been taking tenofovir disoproxil fumarate/emtricitabine and dolutegravir once daily for 10 years, and has an undetectable HIV viral load. He smokes 10 cigarettes per day and has a body mass index (BMI) of 29 kg/m^2. His risk of developing a heart attack or stroke over the next 10 years as calculated by the QRISK®3 algorithm is 14%. He recently developed renal tubular dysfunction attributed to tenofovir use. Until recently the standard options in HIV treatment guidelines included a backbone of two non nucleos(t)ide reverse transcriptase inhibitors. Tenofovir disoproxil fumarate would be inappropriate due to the presence of renal tubular dysfunction and abacavir because of a high risk of cardiovascular event. What are the alternative HIV treatment options available for this man?

What you need to know".

- Antiretroviral therapy regimens containing two active drugs rather than the traditional three or more are now shown to be efficacious in treating HIV.

- Two-drug therapy is a particularly useful option when tenofovir alafenamide, tenofovir disoproxil fumarate or abacavir cannot be used or are not optimal such as in people with high cardiovascular risk, renal impairment or decreased bone mineral density.

- Certain two-drug regimens are used in the setting of switching ART in people who already have an undetectable HIV viral load.

- Two-drug therapy is not suitable for people with HIV and Hepatitis B co-infection or in those with a history of HIV drug resistance or during pregnancy.

- Long-acting injectable two-drug therapy is also available, but this is not suitable in those with a high body mass index, certain viral subtypes, or in those with HIV drug resistance.

1. What is two drug therapy for adults living with HIV?

HIV treatment or antiretroviral therapy (ART) has traditionally consisted of three active drugs (Table 1). In settings where individuals have continued access to HIV care, ART has allowed people with HIV to maintain an undetectable viral load and minimise the immune damage, morbidity and mortality associated with uncontrolled HIV. Contemporary challenges include supporting individuals to maintain optimal adherence to ART and minimizing ART drug toxicity, in particular those associated with the Nucleos(t)side Reverse Transcriptase Inhibitor ART drug class (1) (renal tubular dysfunction (2), osteomalacia (3), and increased cardiovascular risk (4)). To address these challenges, there has been a shift away from the concept of three-drug to two drug ART regimens, thereby reducing the number of drugs used to achieve HIV viral suppression and in so doing, reducing potential drug toxicities and improving adherence.

Current licenced two drug ART regimens recommended by international guidelines include either a boosted Protease Inhibitor (bPI) based or an Integrase strand transfer inhibitor (INSTI) ART, in combination with a non-nucleoside reverse transcriptase inhibitors (NNRTI) or an nucleoside reverse transcriptase inhibitors (NRTI) (Table 2) (5-7). However, the World Health Organisation (WHO) guidelines do not recommend any two drug regimens at present, due to concerns regarding the lack of activity against hepatitis B in those with HIV-hepatitis B co-infection, lack of data in pregnancy, potential drug interactions with TB therapy and the need for baselines HIV resistance testing (8). These concerns are particularly relevant for people living in low- and middle-income settings.

2. How do these drugs work?

The bPI, darunavir, was first approved has been widely used in people with antiretroviral drug resistance since 2006. It works by inhibiting the activity of *HIV-1 protease*, an enzyme which cleaves large HIV gag-pol polyproteins into smaller proteins which are necessary for HIV assembly and RNA packaging resulting in infectious virions (9). Ritonavir boosted darunavir (ritonavir with a second, 'boosted' protease inhibitor enhances patient exposure to the latter) is used in two drug therapy regimens in combination with other drugs including lamivudine, dolutegravir and raltegravir. The development of resistance to ritonavir boosted darunavir is rare (9).

INSTIs prevent the viral enzyme *HIV integrase* from incorporating proviral HIV DNA into the human host cell, inhibiting the HIV-catalyzed strand transfer step of the HIV life cycle (10). The drug structure of second-generation integrase inhibitors, such as dolutegravir, allow extension of the drug molecule further into the target binding site with more flexibility to adjust its position in the presence of amino acid substitutions, allowing the drug to retain antiviral activity in the presence of mutations that confer resistance to first generation integrase inhibitors. Dolutegravir has been used as part of two drug regimens in combination with lamivudine, rilpivirine and ritonavir boosted darunavir. There is no human homolog of viral integrase, making it a specific and effective HIV drug target with excellent tolerability and minimal toxicity (10).

3. How well do the drugs work?

ART naïve individuals

The double-blind phase III randomised controlled trials, GEMINI-1 (N = 719) and GEMINI-2 (N = 722) demonstrated non-inferiority, with a pre-defined margin of 10%, of two-drug regimen of dolutegravir plus lamivudine compared with a three-drug regimen of dolutegravir plus tenofovir diproxil fumarate (TDF) plus emtricitabine at 44 weeks in ART-naive adults (see Table 3) (11). In the pooled intention to treat analysis after 144 weeks, 82% of participants in the two-drug regimen and 84% in the three-drug regimen achieved HIV-1 RNA less than 50 copies per ml (12). Importantly, the inclusion criteria of GEMINI limited enrolment to participants with HIV RNA levels less than 500,000 copies per mL and therefore may not apply to those with higher viral loads (i.e. >500,000 copies per ml). The GEMINI studies also showed that there were potential reductions in tenofovir diproxil fumarate related toxicities with improved biomarkers of bone turnover and renal function in the two-drug regimen arm compared to the three-drug regimen arm (12, 13). Despite potential concerns about the development of drug resistance in two-drug regimen arm, this occurred in only one individual (12).

Studies assessing the efficacy of bPI in two-drug therapy in treatment naïve individuals are emerging. Ritonavir boosted lopinavir in combination with lamivudine (14) and ritonavir-boosted darunavir plus raltegravir have both been shown to be non-inferior to standard three drug therapy in ART naïve individuals. However, ritonavir-boosted darunavir plus raltegravir was only non-inferior to in those patients with CD4 cell counts higher than 200 cells per µL and with baseline HIV-1 RNA of less than 100 000 copies permL (15), while lopinavir remains rarely used in clinical practice due to poor tolerability. Two drug therapy has not been effective with all drugs tested in ART naïve individuals illustrating the importance of the synergy between the drugs included in two drug regimens (16).

ART experienced individuals

Compared to ART-naïve individuals, there is evidence for a larger number of bPI two-drug regimen options for those who are ART experienced and who have already achieved an undetectable viral load and who had no known HIV drug resistance mutation. Ritonavir-boosted protease inhibitors including atazanavir/ritonavir (17, 18), lopinavir/ritonavir (19) and darunavir/ritonavir (20), all in combination with lamivudine, have demonstrated efficacy when compared with standard three-drug regimens in several phase 3 studies of switching ART. However, none of these are available as single tablet combinations and all are boosted with ritonavir, which has a higher number of drug-drug interactions compared to integrase inhibitors.

As in ART-naïve individuals, the two-drug regimen combination of dolutegravir/lamivudine was shown to be safe and efficacious in individuals switching ART in phase 3 randomised control trials. TANGO (N=743) and SALSA (N=493) evaluated a switch to dolutegravir/lamivudine versus continuing a ≥3-drug ART regimen in patients with HIV who were stably suppressed and with creatinine clearance > 30 mL/min/1.73 m^2 (21, 22). Over 90% of participants in the TANGO study were male, while SALSA included more women (39%), and both studies had a low proportion (<20%) of people with African or Asian ancestry.

In the SWORD-1 and SWORD-2 phase III randomised controlled trials, efficacy rates for maintenance of virological suppression of the two-drug regimen (dolutegravir plus rilpivirine) and three-drug regimen were similar (23). A subsequent analysis at week 100 (with no randomised 3-drug comparator arm), efficacy of the two drug-regimen was maintained but

lower at 89% (compared to 95% at week 48), and 7% percent (34/513) (compared to 3% at week 48) of participants had discontinued the regimen because of adverse events (24).

Long-acting injectable agents

Since January 2021, cabotegravir, a second-generation INSTI, has been formulated as a long-acting intramuscular injection, combined with a long-acting injectable formulation of rilpivirine. It is administered as two separate intramuscular injections as a two-month dosing regimen for HIV-1 in virologically suppressed adults(25-27). In March 2022, the oral lead-in period was made optional for adults living with HIV-1 in the US and across Europe (28-30).

In the FLAIR study, a randomised phase III open-label trial lamivudine in treatment-naive patients with HIV-1 RNA suppression, following oral induction therapy with dolutegravir plus abacavir plus lamivudine, maintenance therapy with monthly intramuscular cabotegravir/rilpivirine long-acting regimen was found to be non-inferior to daily oral dolutegravir plus abacavir plus at both 48 and 96 weeks (31, 32). The ATLAS study tested the same intervention in virologically suppressed individuals following an elective switch from a variety of HIV drug classes (33). In contrast, the follow-up ATLAS-2M study reported that cabotegravir/rilpivirine long-acting regimen was efficacious when administered every two months compared to every month (34).

4. How cost-effective is it?

There are potential cost savings with the use of a two-drug regimen; however, the cost of ART varies widely globally, and accurate pricing information is often confidential and subject to local tendering and discount arrangements. The US listed price for 30 days of dolutegravir/lamivudine and dolutegravir/rilpivirine is $3,183 and $3,755, respectively, whereas the UK listed price for both combinations is £656.26 (35, 36). Compared to the monthly cost of standard INSTI containing three-drug regimens (Bictegravir/emtricitabine/tenofovir alafenamide [US $4,301, UK £879.51] and abacavir/dolutegravir/lamivudine [US $4,007 and UK £798.16]), listed two-drug regimen prices are more favourable. Many generic alternatives of HIV drugs are now in use and the inclusion of the individual agents rather than single table regimens may offer additional cost savings. However, no generic single tablet regimens of two-drug therapy are available and this strategy increases pill burden which may not be acceptable for all patients or providers (37, 38).

A recent US study estimated that with 50% uptake of two-drug regimens for ART-naive patients, cost savings approaching $800 million would be possible within 5 years (39, 40). A 2020 Canadian observational study, demonstrated a decrease by 10.3% in ART drug costs when switching from three-drug to two-drug regimens (41). Cost-effectiveness data of the long-acting regimen cabotegravir plus rilpivirine remains approximate, in part due to a lack of clarity around staff and infrastructure costs (42, 43), with current UK guidance suggesting use may be cost-effective only when based on negotiated discounted prices (44).

5. What are the potential harms?

The ART drugs used in two-drug regimens are already widely used as part of three-drug regimens (except for cabotegravir). A key feature of two drug-regimens is the exclusion of abacavir or tenofovir, thereby preventing toxicities associated with these drugs.

Dolutegravir has been associated with weight gain, particularly when taken in a three-drug combination with tenofovir alafenamide (45, 46). Short- and long-term data from the SALSA and GEMINI studies suggest the mean weight gain was numerically higher in the dolutegravir plus lamivudine arms compared to three-arm regiments (usually tenofovir-containing) but that it was not clinically significant (<2 kg difference) (12, 22). Neuropsychiatric side effects are more frequently described in real-world effectiveness studies compared to randomised control trials of dolutegravir, likely related to more restrictive eligibility criteria in efficacy studies. Varying prevalence of insomnia (4-19%), anxiety (2-33%), depression (2-10%) and suicidality (0.1%) have been reported with dolutegravir use in observational studies (47, 48).

The concern about decreased rates of viral suppression has not been demonstrated in studies of oral two-drug regimens. A pooled analysis of phase 3 study data from 1651 participants on injectable long-acting cabotegravir/rilpivirine demonstrated a confirmed virological failure in 1.4% (n = 23/1651) of participants up to 152 weeks, and most of those also developed resistance to one or both drugs (49). Post hoc analysis of the RCTs showed that individuals with a BMI > 30 kg/m^2 and those with clade A1 or A6 subtype virus were most at risk of virological failure, and as such long acting cabotegravir/rilpivirine should be used with caution in these individuals (50). Mild injection site reactions due to intramuscular administration are also common and rarely resulted in discontinuation (51).

Some investigators have expressed concerns about the potential for decreased tissue and central nervous system penetration (52) with two-drug regimens, resulting in low-level viral replication, with subsequent increased immune activation and non-AIDS-related morbidity. However, one recent large international cohort study found no difference in clinical events, including non-AIDS-defining cancers and cardiovascular disease, between two-drug regimens compared to three-drug regimens (53).

6. Can these drugs be given to children and adolescents?

Licenced ART options for children remain limited. While two-drug ART regimens are not currently licenced or recommended for children and adolescents, regimens that utilise dolutegravir or other INSTI, including long-acting injectables, are attractive for this cohort for multiple reasons:

- Children will be taking two nucelos(t)ide reverse transcriptase inhibitors for 10-15 years longer than adults with consequent cumulative toxicity, and in particular, effect on bone mineral density during growth and puberty.
- Two-drug regimens reduce pill burden, dosing frequency, and likely costs, an important consideration given that 90% of children with HIV live in sub-Saharan Africa.
- Use of long-acting two drug regimen options may relieve treatment fatigue and improve adherence, as well as reduce the risk of disclosure and stigma.

The WHO currently recommends the use of dolutegravir-based regimens for children on first and second-line ART. Dolutegravir is associated with a lower potential for the development of ART resistance, high potency at a low milligram dose (leading to smaller tablets) and few drug interactions. The ODYSSEY trial compared dolutegravir-based first and second-line ART

regimens with standard-of-care regimens (either efavirenz or lopinavir/ritonavir-based) in children aged three years or older, most recruited from sub-Saharan Africa (54). The dolutegravir-based ART regimen was superior to standard-of-care regimens in terms of maintaining viral suppression, either used as first- or second-line, and there was no difference in side effects by study arm (55).

Children tend to have higher viral loads than adults and are also more likely to have a history of treatment failure and cumulative resistance, often due to complex psychosocial circumstances, historically fewer robust and limited regimens and drug formulations available, scant pharmacokinetic data and weight-based doing (56). Data on the effectiveness of two-drug regimens in suppressing viral replication compared to three-drug regimens in this cohort remains scarce. SMILE, an open-label non-inferiority trial, recruited virologically-suppressed children aged 6-18 years, comparing an INSTI and boosted darunavir regimen with standard triple regimen(57). Non-inferiority of the two-drug regimen was demonstrated, but there was a significantly higher weight gain of 1.97 kg (95% CI: 1.1, 2.9; $p < 0.001$) and BMI increased of 0.66 kg/m2 (95% CI: 0.3, 1.0; $p < 0.001$)] in the two-drug regimens arm.

Studies have explored the acceptability of long-acting injectables among adolescents, an age group that is documented to have lower adherence rates to ART. A cross-sectional survey of adolescents attending HIV clinics in the USA reported that 88% were willing to use LA injectables (58). There are several reports of viral suppression in youth with HIV with a history of poor adherence receiving long-acting cabotegravir/rilpivirine. (59)

7. What are the considerations for use in resource-limited settings?

Potential benefits of using two-drug INSTI-based regimens in low-middle income countries (LMIC) include reduced toxicity, their antiviral activity in the presence of mutations that confer resistance to first-generation integrase inhibitors and other drug classes, reduction in healthcare utilisation and resource costs, and increased safety. However, most studies on two-drug regimens come from high-income settings.

Baseline resistance testing is not recommended or performed before initiating ART in LMIC, and while transmitted resistance to INSTI is rare, surveillance is needed if dolutegravir is to be rolled out as first-line in LMIC. In addition, there may be baseline HIV drug resistance to the other agents in INSTI-based two-drug regimen, namely lamivudine or emtricitabine, although existing data suggest that the presence of the most common resistance mutation to these drug, M184V/I, does not appear to impact virological outcomes in those on oral two-drug regimens (60-64).

Standard three-drug regimens contain tenofovir which has activity against Hepatitis B, preventing Hepatitis B viral replication and reactivation. Hepatitis B is not systematically screened for in low-income settings, and use of two-drug regimens may leave individuals with Hepatitis B coinfection sub-optimally treated for Hepatitis B, which may lead to compromise future treatment with entecavir. Furthermore, a high proportion of individuals with HIV in sub-Saharan Africa are women of childbearing age, but there remains no data on dual regimens in pregnant women.

Prior to widespread implementation of long-acting injectables cost, prioritisation of patient populations for preferred use, clinic infrastructure requirements, steady supply chains,

decentralization of care, provider and patient training programs, laboratory monitoring, and need to examine patient preferences need to be undertaken. Studies evaluating the implementation of injectable ART in real-world settings are required to inform the scale-up of this approach.

Competing Interests Statement

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests; JT has received speaker fees from Gilead Sciences and conference registration fees from ViiV healthcare. JG has received speakers fee from Janssen UK. BC, RF & SM as per declarations.

Copyright Statement

Author contributions

The work was conceived and planned by JT, BC, SM, JG & RF. The paper was written by JT, BC and RF with input from all authors. JT & RF are guarantors of the paper.

Table 1. Current and historic commonly prescribed antiretrovirals					
Those in **bold** in have been used as part of a two drug ART regimens in either in an ART naïve or switch regimens					
	Nucleoside or nucleotide reverse transcriptase inhibitors (NRTI)		***Non-Nucleoside reverse transcriptase inhibitors (NNRTI)***	***Boosted[a] Protease Inhibitors (bPI)***	***Integrase inhibitors (INSTI)***
Currently Recommended for most people with HIV	tenofovir alafenamide (TAF) tenofovir disoproxil fumarate (TDF)	emtricitabine (FTC)	doravirine (DOR)	**darunavir[a] (DRV)**	bictegravir (BIC) **dolutegravir (DTG)** **raltegravir (RAL)**
	Abacavir[b] (ABC)	**lamivudine (3TC)**			
No longer recommended in all guidelines for all ART Naïve individuals but still in use in switch or people with HIV on stable ART for many years or in certain circumstances			**rilpivirine[d] (RPV)** efavirenz (EFV) nevirapine[e] (NVP) etravirine (ETR)	atazanavir[a] (ATV) lopinavir[a] (LPV)	**cabotegravir[d] (CAB)** elvitegravir (EVG)
No longer routinely recommended	zidovudine (AZT)	stavudine (d4T) didanosine (DDI)			

Notes

A number of less commonly used drugs classes have not been included. Please refer to specific guidelines for complete prescribing information, particularly for pregnancy and children living with HIV.

[a] boosted with ritonavir or cobicistat

[b] only if HLA-B*57:01 negative and HBsAg negative

[c] boosted with cobicistat

[d] Intramuscular CAB/RPV is only approved for people who have achieved viral suppression on another ARV regimen.

[f] Associated with serious and potentially fatal toxicity (hepatic events and severe rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis) in ART naïve individuals

Table 2. International Guidelines Recommendations on two-drug regimens for treatment of HIV

Organisation	Specific two drug agents	Comment
WHO 2019(65)	None	
IAS-USA 2022 (66)	DTG+RPV (AIa)	*None recommended with prior virological failure or transmitted HIV drug resistance HBV co-infections*
	DTG+3TC (AIa)*	
	CAB+RPV (AI)	every 4 weeks (AIa) or every 8 weeks (BI)
US-DHHS 2022 (5)	DTG+RPV (AI),	*None recommended with prior virological failure or transmitted HIV drug resistance HBV co-infections*
	DTG+3TC (AI)*,	if HIV RNA<500,000 copies/mL)
	DTG+DRV/r (CI)	
	DRV/r once daily plus 3TC (CI)	
	PI/b+3TC (with ATV/r (CI) or LPV/r: (CI), with DRV/r: (BI)),	
	DRV/r plus RAL twice a day (CI)	if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm3
	LA ART, CAB+RPV (AI) every 1 or 2month	Only suitable for those who are engaged with their healthcare, virologically suppressed on oral therapy for 3 to 6 months, and who agree to make the frequent clinic visits needed to receive the injectable drugs
EACS 2020 (26)	DTG+RPV, 3TC+DTG*, 3TC+DRV/b, 3TC+ATV/b (large RCT or meta-analysis) DRV/b+RPV, (small trials) DRV/b+DTG (small trials)	HIV-VL <50 copies/ml for the past 6 months, no historical HIVDR, absence of chronic HBV co-infection
BHIVA 2022 (27)	3TC+DTG*(A1),	No baseline lamivudine resistance Baseline viral load <500,000 copies/mL and CD4 count >200 cells/mm
	DTG+RPV (A2),	Studied only in suppressed switch; high risk of NNRTI resistance at virological failure

	LA ART, CAB+RPV (A1)	Studied only in suppressed switch; high risk of NNRTI and INSTI resistance at virological failure
	DRV/b plus RAL twice a day	Underperformed at viral load >100,000 copies/mL and CD4 count <200 cells/mm3 when used first line
	DRV/b+DTG	
	PI/b+3TC (1A) (with ATV/r or LPV/r or DRV/r)	
Paediatric Guidelines (26, 67)	US DHSS: Early findings from the PENTA-17 SMILE study evaluating darunavir/ritonavir (DRV/r) combined with an INSTI found that DRV/r plus an INSTI was non-inferior in maintaining virologic suppression at 48 weeks in participants without INSTI or protease inhibitor (PI) resistance.14 Although the Panel does not recommend this combination for initial treatment, it might be considered in situations in which simplification or avoidance of NRTIs is desired. US DHSS: Long-acting injectable antiretroviral medications may be considered a treatment simplification approach for some virologically suppressed adolescents. The co-packaged, two-drug injectable ARV regimen of cabotegravir and rilpivirine (CAB and RPV; Cabenuva) is approved by the U.S. Food and Drug Administration for use in children weighing ≥35 kilograms and ≥12 years of age, with viral suppression (defined as <50 copies/mL), on a stable ARV regimen, without a history of treatment failure, and without known or suspected drug resistance to either drug EACS: Dual therapy is not recommended in first line or for simplification but can be considered on a case-by-case basis in adherent children and adolescents living with HIV	

*only combination recommended in the ART naïve setting

/r/b/c, ritonavir/boosted/cobicistat; 3TC, lamivudine; ATV, atazanavir; CAB, cabotegravir; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; HBV, hepatitis B virus; HIVDR, HIV drug resistance; INSTI, integrase strand transfer inhibitor; LA, long-acting; NNRTI, non-nucleotide reverse transcriptase; NRTI, nucleos(T)ide reverse transcriptase; RAL, raltegravir; RCT, randomized controlled trial; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VF, virological failure; VL, viral load.

[b]Strength of recommendation: A (strong), B (moderate), C (limited) – quality of evidence: I (data from ≥1 RCT), II (data from well-designed nonrandomized clinical trials or cohort (observational with long-term outcomes) or case–control studies), III (expert opinion) and a (published in a peer reviewed journal), b (presented in abstract form at peered-reviewed scientific meetings).

Footnotes
DTG/3TC is the only 2-drug regimen currently recommended for initial therapy only if HIV RNA <500 000 copies/mL and HBV coinfection not present (evidence rating: AIa)
Not Recommended to Initiate During Pregnancy Because of Inadequate Data to Support Use (Evidence Rating: AIII for All)
DTG/3TC is not recommended with rifampin because of drug-drug interactions and inadequate data (evidence rating: BIII)

*The two licenced **single tablet two regim**ens are:*
i. dolutegravir 50mg and lamivudine 300mg (Dovato)) - licenced for both treatment initiation and switches.

ii. dolutegravir 50mg and rilpivirine 25mg (Juluca)) - licenced as a switch agent in individuals already suppressed on ART

- *They should only be used in those without known major HIV drug resistance mutations.*
- *The omission of tenofovir from two drug ART regimens means that these regimens are also unsuitable for people with no immunity to or those with hepatitis B co-infection.*
- *Due to the absence of data in key groups such as pregnant women, these agents are not currently recommended in pregnancy.*

Table 3. Randomised control trials of Two Drug Therapy for people living with HIV

2 Drug Therapy regimen†	***Treatment Naïve Studies***	***Switch Studies***	***Recommended* for ART Naïve individuals***	***Recommended* in ART Switch individuals***
Dolutegravir plus lamivudine (oral)	***GEMINI-1 GEMINI-2 (11, 12, 68)***	***SALSA(22) TANGO(21)***	***Yes*** *except for individuals with HIV RNA >500,000 copies/mL*	***Yes***
Darunavir/ritonavir plus raltegravir (oral)	***NEAT001 ANRS143 (15, 69)***	-	***Maybe*** *In certain circumstance* and if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm3*	***No***
Darunavir/ ritonavir plus lamivudine (oral)	***ANDES(70)***	***DUAL-GESIDA (20)***	***Maybe*** *Supported by a single unpublished study*	***Yes***
long-acting cabotegravir plus rilpivirine (intramuscular)	***FLAIR(31)***	***ATLAS-2M (33)***	***Yes, but requires an oral lead-in phase***	***Yes***
Dolutegravir plus rilpivirine (oral)	-	***SWORD 1 SWORD 2(23, 24)***	***No***	***Yes***
Atazanavir plus ritonavir (oral)	-	***SALT(18) ATLAS-M(17)***	***No***	***Yes***
Dolutegravir plus darunavir/ritonavir (oral)	-	***DUALIS(71)***	***No***	***Yes*** *recommended only in the absence of other alternative options*
Lopinavir/ritonavir plus Lamivudine (oral)	-	***OLE(19)***	***No***	***Yes***
2 Drug Therapy regimen studies in Paediatric populations**	PENTA-17 SMILE study evaluating darunavir/ritonavir (DRV/r) combined with an INSTI, including 318 children aged 6 to 18 years, found that DRV/r plus an INSTI was non-inferior in maintaining virologic suppression at 48 weeks in participants without INSTI or protease inhibitor (PI) resistance (57). Other trials			

	of dolutegravir-based two drug therapy in children such as DANCE (NCT03682848) and D3 (PENTA 21) (NCT04337450) are ongoing and will contribute to the evidence base as well as data to facilitate the timely approval of dolutegravir fixed drug paediatric formulations. Several ongoing studies are investigating the pharmacokinetics and safety and effectiveness of LA two drug ART regimens in adolescents, such as the More Options for Children and Adolescents (MOCHA; NCT03497676) study.

† none of the two-drug regimens discussed have adequate anti-HBV activity, these regimens are not recommended for individuals with HBV coinfection or in women who are pregnant

*as recommended in IAS, DHHS and EACS HIV treatment guidelines

** not recommended for use in current guidelines

Footnotes:

Tips for patients

- Some HIV treatments can contribute to health problems or unwanted side effects that are seen more commonly in all people as they get older, such as kidney, bone, and heart problems. In certain circumstances, it is now possible to treat HIV with two drugs rather than the traditional combinations which contained three drugs or more. This means we can remove drugs from people's treatment that may contribute to other health problems or to unwanted effects.
- HIV treatment using two-drug regimens may also be appropriate to reduce the risk of certain drug interactions. However, there are still some important drug interactions even with two-drug therapy and it is important to check with your prescriber. For example, some minerals present in multivitamins, supplements and antacid preparations, such as magnesium, calcium, zinc, and iron, can decrease dolutegravir levels if taken at the same time.
- It is still very important to take treatment around the same time every day with two-drug regimens.
- The first long-acting injectable treatment for HIV is now available in the US and Europe. It is given either every one or two months, depending on the county you live in

Education into practice

Question about practice:

- Do you regularly check for drug-drug interactions in people with HIV?
- Has your department assessed whether two-drug or long-acting injectable regimens would be feasible in community or primary care settings?

Audit Suggestion

- How many people living with HIV in your practice have been started on or switched to a two-drug regimen in the past year.
- How many people living with HIV in your practice would be eligible for and interested in long-acting antiretroviral therapy.

Reflective question

Thinking about the last time you had a consultation a person living with HIV. Did you consider the impact of their antiretroviral therapy on any co-morbid conditions such as cardiovascular or renal disease?

How patients were involved in the creation of this article

This article was co-produced by people living with HIV. Members of the UK Community Advisory Board, a network for community HIV treatment advocates across the UK, contributed to its production, and all aspects of the article.

Box: The perspective of people living with HIV on the current state of anti-retroviral therapy

Considerations around two drug therapy

- Some individuals experience debilitating side-effects from ART, such as insomnia and weight gain.
- People of different ethnicities and genders respond differently to some anti-retroviral therapies. For example, efavirenz levels in people of African ancestry are much higher than in others and integrase inhibitors lead to significantly more weight gain in women than in men.
- More people are now ageing with HIV, which can lead to potential issues with drug interactions when other medicines are needed to deal with conditions associated with ageing, such as high cholesterol, high blood pressure, and diabetes.

Long-acting agents may be particularly useful for:

- People who struggle emotionally with the daily reminder that ART gives about their HIV status.
- People with complex or unpredictable lifestyles, such as those who are homeless or who use intravenous drugs, and who may not have the daily structure needed for oral ART regimen.
- Those with concerns around confidentiality and disclosure of diagnosis, for example people in shared accommodation such as in detention centres and prison, who want to keep their HIV status to themselves and may struggle to keep their tablets securely and in confidence.

  Supply issues may lead to issues with daily adherence in a resource-limited setting.

Box/table: Tips for Safer ART Prescribing and monitoring

No additional monitoring requirements are needed for oral two drug therapy. HIV viral loads should be measured every six months. For long-acting cabotegravir/rilpivirine, HIV viral load should be measured every two months

Drug-Drug interactions are common with drugs used in two drug ART regimens. It is recommended to use an interaction checker such as https://www.hiv-druginteractions.org/checker. A list of some commonly encountered drug interactions is listed below

Dolutegravir may interact with:	
Metformin	co administration may result in potential increased exposure to metformin. Close monitoring is recommended when starting or stopping Metformin in combi - nation with dolutegravir as a dose adjustment of metformin may be required.
Polyvalent Cations, including Calcium, Iron (oral) and Magnesium	ART should be administered 2 hours before or 6 hours after taking medications containing polyvalent cations, such as antacids
Rifampicin	A dose adjustment of dolutegravir to 50mg twice daily is recommended when dolutegravir is co administered with Rifampicin

Rilpivirine may interact with:	
Antacids	The combination of rilpivirine and antacids should be used with caution as co-administration may cause significant decreases in rilpivirine plasma concentrations due to an increase in gastric pH. Antacids should be taken well separated in time from the administration of RPV/DTG (minimum 6 hours before or 4 hours after).
Protein Pump Inhibitors	Co-administration is contraindicated due to the potential for significant decreases in rilpivirine plasma concentrations due to gastric pH increase
Rifampicin	A dose adjustment of dolutegravir to 50mg twice daily is recommended when dolutegravir is co administered with Rifampicin
Ritonavir Boosted Protease Inhibitors Protease inhibitors (PIs) are metabolized in the liver by CYP3A isoenzymes; therefore, their metabolism may be altered by CYP inducers or inhibitors. Therefore, there are many DDIs associated with this drug class. Some of the common interactions are listed below. However, an interaction checker should be used to interrupt the potential DDIs such as https://www.hiv-druginteractions.org/checker	

Statins	The key drug interactions between antiretroviral medications and statins occur with the statins that are metabolized through the CYP3A4 pathway (simvastatin, lovastatin, and atorvastatin) when taken concomitantly with the potent CYP3A inhibitors ritonavir or cobicistat.
Corticosteroids	This complication results from ritonavir-mediated inhibition of CYP3A4 enzymes, which increases the levels of certain corticosteroids that are also metabolized via CYP3A enzymes. Most cases of ritonavir-associated adrenal suppression have involved fluticasone, but other corticosteroids, such as budesonide and mometasone may also interact . Most of these cases have involved oral, nasal or inhaled corticosteroids, but recent reports have also described this complication with corticosteroids delivered through topical and injectable ocular preparations, as well as following intrabursal, intraarticular, and epidural injections
Rifampicin	Coadministration is contraindicated
Calcium Channel Blockers	bPIs increases drug concentrations of calcium channel blockers. These cardiac medications can generally be used, but with caution, starting with low doses.
Proton Pump Inhibitors	For patients taking ritonavir-boosted darunavir, the omeprazole dose (or omeprazole equivalent dose) should not exceed 40 mg daily.
Antipsychotics	Anripsychotic levels may be increased by bPI
DOAC	DOAC Levels may be increased by bPI
Phosphodiesterase Type 5 (PDE5) Inhibitors	PDE5 Inhibitor levels may be increased when co administered with a bPI
Anticonvulsants	Several anticonvulsant medications significantly lower antiretroviral drug levels, potentially leading to virologic failure. Among possible options for use of an anticonvulsant medication in persons on antiretroviral therapy, levetiracetam is considered the antiepileptic of choice due to its broad spectrum of activity, minimal drug interactions (since it is not metabolized via any CYP450 pathway).

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