BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022

Public consultation comments

Compilation of all comments received via the BHIVA website and during the community consultation. The writing group thanks everyone who responded to the consultation. The guidelines have been revised based on the comments unless otherwise stated

Contents

	Name	Affiliation	Comments	Writing group response
	Jonathan Cartledge	CNWL	Starting ART in patients with AIDS defining illness The Zilopa study I has poor representation of some OIs particularly toxo where I would have real concerns about initiating ART without assessing response and risk of coning if IRIS occurred I feel the recommendation is too directive I would happier with a clause to include “after consideration of the risks of IRIS in consultation with colleagues with HIV inpatient experience”	The incidence of IRIS in patients with toxoplasmosis is low and does not appear to be higher in people who initiate ART early (van Bilsen, AIDS 2017; 31: 1415-24, Schafer, AIDS Res Ther 2019; 16: 34). Hence, the recommendation that most individuals initiate ART within 2 weeks of starting antimicrobial chemotherapy for an AIDS-defining or other major

				infection can also be applied to those with toxoplasmosis
			Given that the recommended starting regimens are all INSTI based I would recommend baseline resistance testing for INSTI resistance	This is the remit of the monitoring guidelines and not indicated outside the current recommendations
	Nicolo Girometti	56 Dean Street, Chelsea and Westminster NHS Foundation Trust	First and foremost I wanted to manifest my appreciation for the great work behind the creation of our national BHIVA guidelines. This last update reviews topics which are very poignant and successfully manages to provide clarity to some aspects where data were lacking so far. I have a couple of comments I wanted to share with you, confident that you will take them into consideration and make the use you deem more appropriate (could well be to trash them in the bin!!). I wanted to evidence some newer data we published about rapid ART initiation in a real-life setting in the UK, which could increase evidence in favor of starting ART (https://doi.org/10.1111/hiv.12900), as discussed in paragraph 4.2. We analyzed virologic outcomes and retention in care rates in an urban (London) cohort of patients (n=153) diagnosed with early HIV infection who went on starting ART shortly after the HIV diagnosis (median time 6 days, IQR 10-14d). 26 individuals started ART the same day they were diagnosed with HIV. TDF/FTC was prescribed along with DRV/b (78%) or INSTI (22%). We observed full retention in care at 24 weeks from ART start and a significantly faster viral load suppression when INSTI were used. I also wanted to highlight some data on rapid ART start in people with recent / ongoing PrEP exposure, which could support the statement in paragraph 5.8. We recently published real life data (AIDS 2022, 36:561–566) on virologic outcomes in patients newly diagnosed with HIV-1 whilst on TDF-PrEP or recently exposed to PrEP (n=52). Despite yielding a high proportion of M184V mutation, those who started ART (n=47) all went on achieving viral load suppression at week 24, following intensification of PrEP into ART with mostly either DRV/b, DTG or BIC as third agent. Median time from HIV-1 diagnosis to ART start was of 8 days (IQR 6-14d). I believe this supports the quick intensification of PrEP into full ART, reassuring the clinician in doing so with no hesitations or need to wait for the genotypic test results to be back.	Thank you Thank you - sentence and reference added Thank you - sentence and reference added

			Thank you for all the hard work put in to realize guidelines which are so helpful for our day to day practice!	Thank you again
	Tristan Barber	Royal Free	First of all I'd like to commend all authors on this incredible, extensive, comprehensive guideline, and for all the tremendous hard work that must have gone in to compiling this document. I have tried to keep comments at this stage to an absolute minimum. My one overarching comment is that I wonder if, now, for future iterations, this guideline can and should be split into two? One would be the 'general principles to HIV/ART management' and would include all the advice on, for instance, starting therapy, stopping therapy, managing failure, constructing regimens in those with limited options, adherence, and so on. All of this is absolutely fantastic but may need updating less often than the drugs themselves where things evolve more rapidly than strategic approaches to ART. This would leave the second document being the 'specific' ART guideline, relating to drug options and choices only – for initial therapy, stable switch, etc. This document could be subject to a more regular review and be more quickly updated. I am sure the group and the guidelines subcommittee have considered some of these points already but think this might align most to where the data changes most frequently, and where there is a need to update UK guidelines more often. My specific points: P16 'Symptomatic primary HIV' – suggest include all those with primary HIV, including those w symptoms for definite (would then align with p19 section 4.4) P32 Section 5.1 I'd urge that ABC/3TC/DTG is considered as an alternative regimen for initial ART. Firmly believe that ABC adds little other than side effects and possible harm, and inclusion of ABC/3TC/DTG may be preferred by those who elect for 3DR over 2DR against the available evidence. PWH may therefore be at risk of short term side effects and long term toxicity from unnecessary ABC prescribing.	Thank you Thank you, a great suggestion – we will pass this comment on to the guidelines subcommittee and the next ART guidelines chair Thank you - amended accordingly Based on our GRADE analysis and Forest plots this remains a recommended regimen. Short-term tolerability and CVD risk are not considered critical endpoints for this guideline, a section has been added on abacavir and CVD risk, including advice to not start ABC in someone with a CVD risk >10% over 10 years, and clinicians should take this into account when discussing ART choice. In addition,

				ABC/3TC/DTG has been compared with several other regimens in RCTs whereas DTG/3TC has only been compared with TDF/FTC + DTG first line
			P47 Section 5.2 Not sure much evidence for ABC/3TC + DOR? Ditto ABC/3TC + RPV? Personal preference would be to see DTG/3TC higher up the list of options here for those in whom it is suitable, but appreciate options presented in a logical order.	22% in the DOR vs DRV/b study were on an ABC/3TC backbone but, regardless, we do not recommend any RPV-based ART first line. Assuming this refers to table 5.2 rather than section 5.2 we do not believe there is sufficient evidence to recommend switching from ABC/3TC + DOR or RPV, nor to recommend against it if is deemed the most clinically appropriate option
			Thanks again to all involved , and for considering these comments and thoughts also. One supplementary comment in addition to those submitted previously. P35. Appreciating there is little evidence I am not sure this statement should be included for DTG/3TC as initial therapy: • It is not suitable for those with HIV-related cognitive impairment Whilst in those who develop cognitive impairment when virally suppressed I agree that switching to more novel regimens without an evidence base to support their use in this situation would be incorrect, I think in the context of someone who is ART naïve it is arguable that any suppressive ART is likely to improve their cognition. In this scenario I therefore feel the balance should be in favour of using ART that will be suppressive, including DTG/3TC as a possible option. If cognitive impairment persists despite a period of viral suppression then the individual should be managed according the other recommendations given.	Thank you for this comment. At the time of writing, there are insufficient data to recommend the use of dual therapy in persons with HIV with HIV-associated cognitive impairment and this cannot be recommended
	William Hickey; Nipur Siani	MSD UK	MSD welcomes the opportunity to consult on the draft BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 (2022). MSD supports the development of evidence-based guidelines and appreciates all of the extremely hard work that has gone into producing this detailed draft.	Thank you

			Please see below for detailed comments by section. 5.3 Regimens recommended in certain clinical situations: The rationale for recommending doravirine-based ART only for certain clinical scenarios is the current lack of comparison with INSTIs. MSD requests the writing committee to consider recommending options from different antiretroviral classes as initial treatment for most people living with HIV (PLWH). Providing options from different antiretroviral classes will allow treatment to be individualised to the need of the person living with HIV. Currently, lifelong treatment is required for HIV-1, therefore it is important to safeguard against treatment related toxicity and comorbidity in addition to virological success and failure. NHS England's decision to make doravirine available for both therapy-naïve individuals and those requiring a switch to alternative treatments is underpinned by the NICE Clinical Commissioning Support Team's Evidence Review for doravirine, reviewing data from studies conducted when protease inhibitor (PI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens constituted standard of care. At the time of the DRIVE-FORWARD and DRIVE-AHEAD trial designs (2014-2015), boosted darunavir and efavirenz respectively were recommended first line in multiple international HIV treatment guidelines (BHIVA 2014 and EACS 2014 guidelines). Ritonavir-boosted darunavir was chosen as the comparator in DRIVE-FORWARD because it is widely regarded as the most robust third agent with respect to virological efficacy and treatment failure with resistance. The safety and efficacy of doravirine in treatment naïve adults has been presented through to 4 years of experience from the DRIVE-FORWARD and DRIVE-AHEAD clinical trials. Through to week 192, doravirine has shown a favourable efficacy and safety profile over 4 years. Doravirine has shown low rates of serious drug related adverse events (3 [0.8%] and 2 [0.5%] in DRIVE-FORWARD and DRIVE-AHEAD, respectively) and discontinuation due to serious drug related adverse effects (1 [0.3%] in DRIVE-FORWARD and DRIVE-AHEAD). Modest weight changes were seen through week 192 with a median of approximately 2kg weight increase in both trials. Given the demonstrable long-term efficacy and safety of doravirine-based ART regimens in treatment naïve adults, NHS England's commissioning decision, and	Thank you. We appreciate these detailed comments but the reality is that doravirine has only demonstrated non-inferiority to efavirenz and darunavir/r, neither of which are recommended for most. Based on NICE-approved methodology and critical endpoints selected by the writing group, doravirine remains recommended but not for most. We have outlined key advantages over efavirenz and darunavir in the text and note that the inclusion of efavirenz is for a very limited population, so arguably 'less' recommended than doravirine

			the benefits of enabling individualised treatment, MSD would request that the writing committee consider including doravirine as an initial treatment for most people living with HIV. References: Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018; 5: e211–20. Molina JM, Squires K, Sax PE et al. DRIVE-FORWARD trial group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV. 2020 Jan;7 Molina HM, Orkin C, Chan P et al. Safety and efficacy of doravirine in treatment naïve adults with HIV-1: 4 years of experience from the DRIVE FORWARD and DRIVE AHEAD clinical trials. EACS 2021, October 27-30. 5.3 Regimens recommended in certain clinical situations: Doravirine has shown broadly similar outcomes to efavirenz and boosted darunavir, whereas recommended INSTIs have shown superior outcomes to these agents. MSD requests that the writing committee review the recommendation that doravirine-based ART should be reserved only for certain clinical scenarios in treatment naïve adults by reconsidering the statement that doravirine has broadly similar outcomes to efavirenz and boosted darunavir, whereas recommended INSTIs have shown superior outcomes to these agents. This is based on the following data. • In DRIVE-FORWARD at week 48 and week 96, the effect of doravirine on fasting lipid concentrations was superior to that of ritonavir-boosted darunavir, as shown by significant between-treatment differences for the mean change from baseline in LDL-cholesterol and non-HDL-cholesterol concentrations. • In DRIVE-AHEAD at week 48, doravirine has demonstrated superior neuropsychiatric tolerability and superior lipid profile compared to EFV/FTC/TDF. This favourable safety profile continued through week 96. • In DRIVE-FORWARD, at the week 96 secondary efficacy endpoint, a higher	Thank you - our analysis is based on pre-determined critical endpoints and many of those listed are not critical endpoints. We have already highlighted doravirine's superior neuropsychiatric profile vs efavirenz and have added a line about lipids. We already acknowledge the superior lipid/GI profile vs darunavir

			proportion of the doravirine group (277 [73%] of 383) achieved an HIV-1 RNA concentration of < 50 copies per mL than the darunavir group (248 [66%] of 383); difference 7.1%, 95% CI 0.5–13.7). This is important to highlight as this difference of 7.1% has a lower bound 95% confidence interval above zero, with upper bound confidence interval above 10% (pre-specified non-inferiority margin). Given the superior lipid and neuropsychiatric profile demonstrated by doravirine, and the higher risk of both neuropsychiatric and cardiovascular disease amongst People Living with HIV in the UK (evidence base highlighted below), MSD would urge the guideline committee to recommend doravirine as first line treatment for most People Living with HIV. • A 2022 publication in the Journal of Infectious Diseases, Gooden at al reports that in the UK, People Living with HIV have an increased risk for composite cardiovascular disease, stroke, ischemic heart disease, hypertension, type 2 diabetes, chronic kidney disease, and an approximately 3-fold risk for all-cause mortality. • A systematic review published in 2018 by Chaponda et al, showed that amongst People Living with HIV in the UK, the prevalence of depression varied from 17–47%, compared with a reported 2–5% prevalence for the UK general population. Similar disparities were observed in the higher prevalence of anxiety, depression or anxiety, difficulty sleeping, and suicide ideation amongst People Living with HIV. MSD would also request that the guideline committee apply caution when making conclusions based on results across clinical trials with significant design differences. Below are some of the differences in the trials referenced in these BHIVA guidelines that compare doravirine to efavirenz and ritonavir-boosted darunavir and dolutegravir to efavirenz and ritonavir-boosted protease inhibitor. • In DRIVE-FORWARD and DRIVE-AHEAD, Protocol Defined Virological Failure (PDVF) was defined as either non-response (two consecutive measures at least 1 week apart of confirmed HIV-1 RNA c≥200 c/mL at week 24 or 36, or confirmed HIV-1 RNA of ≥50 copies per mL at week 48) or rebound (two consecutive measures at 1 week apart of confirmed HIV-1 RNA ≥50 c/mL after an initial response of HIV-1 RNA • DRIVE-FORWARD and DRIVE-AHEAD are double blinded studies through to week 96. Two out of the three studies comparing dolutegravir to efavirenz, and both studies that compare dolutegravir to boosted protease inhibitor are open	EFV is not recommended beyond pregnancy or TB treatment so, arguably, although both are recommended in certain clinical situations, the EFV recommendation is much more restricted already We agree that people with HIV may experience a higher burden of comorbidities but these were not considered to be critical endpoints and there is a lack of data from well-designed cohorts that doravirine is associated with a lower risk of these. We encourage Merck to support analyses exploring the relative impact of doravirine on age-related comorbidities and any new data will be considered in the next ART guidelines update. There is no high-quality evidence that doravirine is associated with a lower risk of neuropsychiatric symptoms than INSTIs We do not dispute the relative advantages of DOR over DRV/b or EFV but the non-inferior efficacy against these two agents, and lack of comparison against the options recommended for most, renders DOR as an option for some. DOR is still recommended, just not for most, so where a clinician, in partnership with the patient, deems DOR the most clinically appropriate option, DOR is a recommended option still

			label studies, with differences in pill count seen across arms. Based on a NICE Evidence Review of the DRIVE-FORWARD and DRIVE-AHEAD trials, NHS England made the decision to make doravirine available for people living with HIV in both naïve and switch clinical scenarios. Similarly, doravirine was also recommended for unrestricted use (within the marketing authorisation) following robust assessments of clinical and cost-effectiveness by the Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG) respectively. Given the efficacy and safety of doravirine-based ART regimens demonstrated in treatment naïve adults through 4 years, NHS England's, Scottish Medicines Consortium, All Wales Medicines Strategy Group commissioning decision, and the benefits of enabling individualised treatment, MSD would request that the writing committee consider including doravirine as an option from a different antiretroviral class as initial treatment for most people living with HIV. References: Molina JM, Squires K, Sax PE, et al. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 48-week results of a randomised, double-blind, phase 3, non-inferiority trial. Lancet HIV 2018; 5: e211–20. Molina JM, Squires K, Sax PE et al. DRIVE-FORWARD trial group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV. 2020 Jan;7 Orkin C, Squires KE, Molina JM et al. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) Versus Efavirenz/Emtricitabine/TDF in Treatment-naive Adults with Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial. Clin Infect Dis. 2021 Jul 1;73(1):33-42. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014 Jun 28;383(9936):2222-31. doi: 10.1016/S0140-6736(14)60084-2. Epub 2014 Apr 1. Erratum in: Lancet. 2015 Jun	DOR is an option for initial treatment, but based on NICE-approved guidelines methodology and our pre-determined critical endpoints, it is not recommended for most

			27;385(9987):2576. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. Lancet HIV. 2017 Dec;4(12):e536-e546. doi: 10.1016/S2352-3018(17)30095-4. Epub 2017 Jul 17. Erratum in: Lancet HIV. 2017 Dec;4(12):e535. Gooden T, Gardner M, Wang J, et al. Incidence of Cardiometabolic Diseases in People With and Without Human Immunodeficiency Virus in the United Kingdom: A Population-Based Matched Cohort Study. The Journal of Infectious Diseases. 2022;225:1348–56. doi: https://doi.org/10.1093/infdis/jiab420 Chaponda M, Aldhouse N, Kroes M, et al. Systematic review of the prevalence of psychiatric illness and sleep disturbance as co-morbidities of HIV infection in the UK. International Journal of STD and AIDS. 2018. doi:https://doi.org/10.1177/0956462417750708	
			5.3 Regimens recommended in certain clinical situations : Raltegravir is recommended only in certain clinical scenarios based on the underperformance in terms of virological success for raltegravir compared to dolutegravir among people with a baseline viral load >100,000 copies/ml MSD requests the writing committee to reconsider recommending raltegravir only in certain clinical scenarios specifically only among people with a baseline viral load < 100,000 copies/ml. SPRING-2 at week 96 showed 332 (81%) of 411 patients in the dolutegravir group and 314 (76%) of 411 patients in the raltegravir group had HIV-1 RNA less than 50 copies per mL (adjusted difference 4.5%, 95% CI –1.1% to 10.0%) confirming non-inferiority. Secondary analyses of efficacy such as per protocol (HIV RNA SPRING-2 was not powered for a stratified viral load comparison and therefore MSD requests the writing committee to reconsider the use of this trial to make the recommendation on using raltegravir only among people with a baseline viral	Our own analyses, undertaken using NICE-recommended GRADE methodology, reveal underperformance of RAL at high baseline viral loads Despite lack of power, there was a statistically significant underperformance of RAL at higher viral load. Our recommendation remains unchanged

			load References: Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013 Nov;13(11):927-35. doi: 10.1016/S1473-3099(13)70257-3. Epub 2013 Sep 2 Absence of RAL 400mg as a first line choice in pregnancy MSD requests the writing committee to consider the recent update to the marketing authorisation for raltegravir 400 mg to allow it to be used twice daily during pregnancy if clinically needed. A large amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the first trimester (more than 1,000 prospective pregnancy outcomes) indicates no malformative toxicity. Animal studies have shown reproductive toxicity. Raltegravir was not teratogenic in developmental toxicity studies in rats and rabbits. A slight increase in incidence of supernumerary ribs, a variant in the normal developmental process, was observed in rat foetuses of dams exposed to raltegravir at approximately 4.4-fold human exposure at the recommended human dose (RHD) based on AUC0-24 hr. No development effects were seen at 3.4-fold human exposure at the RHD. Similar findings were not observed in rabbits. A moderate amount of data on pregnant women with exposure to raltegravir 400 mg twice daily during the second and/or third trimester (between 300-1,000 prospective pregnancy outcomes) indicates no increased risk of feto/neonatal toxicity. MSD appreciate the BHIVA treatment guidelines in line with the BHIVA guidelines for the management of HIV in pregnancy and postpartum recommend efavirenz as a first line choice in pregnancy due to having the most safety data in pregnancy. However, the marketing authorisation for efavirenz currently recommends efavirenz should not be used during pregnancy unless the patient's clinical condition requires such treatment. MSD requests the writing committee makes clear in these guidelines that raltegravir 400mg is an option during pregnancy if clinically needed. References:	We clearly signpost people to the pregnancy guidelines so have not added further detail. We have highlighted that pregnancy is one of the limited scenarios where EFV could be a preferred choice first line, that is all

			Summary of product characteristics: Raltegravir 400mg [Online] Available at https://www.medicines.org.uk/emc/product/6171/smpc [Accessed online May 2022] 5.10 Suppressed switch or maintenance: Table 5.2 Recommendations for choice of ART for suppressed switch or maintenance. MSD acknowledge that a statement appears above Table 5.2 specifying All regimens recommended for first-line ART are also recommended for suppressed switch or maintenance. In addition, the following regimens are also acceptable. However, Table 5.2 lists some of the regimens recommended for first line ART but not others such as tenofovir-DX/emtricitabine or tenofovir-AF/emtricitabine with raltegravir. MSD requests the guidelines writing committee to consider for consistency/clarity to include all regimens recommended for first line ART.	Thank you for highlighting this oversight - all options recommended first line are also included as options for suppressed switch
	Farhan Omar		My name farhan Omar olive my country somali land I'm positive hi v 1992 to 2022/ one day I'm not using medical HIV I'm drinking some traditional oil two spon aday I'm 75gm	Thank you for your comments
	Rory Grier Gavin	HIV Pharmacy Association	Overall, a very well written and comprehensive guideline. We would like to highlight/query the following points. 1.5 Implications for research (page 11) Could include a statement in this section to promote the participation of women and minority groups in clinical trials/research. 6.2.2 Stopping therapy: pharmacological considerations (page 75) Unclear why only efavirenz and nevirapine are highlighted in terms of covering the PK tail with DRV/r when etravirine and rilpivirine have similar PK tails. 6.2.3.3 Switching from efavirenz, etravirine or nevirapine to long-acting cabotegravir/rilpivirine (page 78) 4-weekly intramuscular cabotegravir/rilpivirine is recommended for the first	Thank you Thank you - sentence added Thank you, we have added etravirine. Rilpivirine is not an inducer so has not been included Thank you – on reflection we agree and have removed this recommendation

			three months when switching from efavirenz- or etravirine-based therapy (GPP). However residual induction effects of EFV and ETR are expected to persist for up to 2 weeks after discontinuation and during the 4-week OLI, one recommended option for mitigating this residual induction is to give double dose PO RPV for 2 weeks then standard dose PO RPV for 2 weeks (in combination with standard dose PO CAB for the 4-week OLI). It is therefore unclear why 4-weekly injections are required for the first three months as any residual induction should have subsided before starting the IM injections. 8.2 Chronic kidney disease eGFR is used throughout this section e.g. page 114 states tenofovir-AF should not be used if eGFR if eGFR <30 mL/min/1.73 m2. Many ARV SPC's (including tenofovir-AF) renal impairment advice is based on creatinine clearance using the Cockcroft and Gault equation. If the writing group are happy for eGFR and CrCl to be used interchangeably, then a statement should be included to this effect or alternatively a statement to follow local advice on measuring renal impairment. Thank you.	Of note, the renal prescribing advice for many ARVs is based on creatine clearance estimated by the Cockcroft–Gault equation. We advise following local guidelines when making decisions about ART prescribing
	Gil Reynolds Diogo	Janssen	Thank you for providing the opportunity to review and comment on the new BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022. Janssen have one comment we would like to register please. Relating to page 37 point 5.3.3 Darunavir/ritonavir we would like to propose the expansion of the safety commentary and inclusion of a statement relating to the adverse event types: Tolerability and safety were much the same in each group. Of the commonly reported clinical adverse events, diarrhoea was more common in the darunavir plus ritonavir group than in the dolutegravir group, whereas headache was more common in the dolutegravir group than in the darunavir plus ritonavir group. The most common drug-related adverse events were diarrhoea (23/242 [10%] in the dolutegravir group vs 57/242 [24%] in the darunavir plus ritonavir group), nausea (31/242 [13%] vs 34/242 [14%]), and headache (17/242 [7%] vs 12/242 [5%]). At 96 weeks, the incidence of serious adverse events was higher in the	Thank you Thank you. We will clarify and add detail to the differences seen in discontinuation due to adverse events and serious adverse events at relevant timepoints The writing group did not consider drug-related adverse events of any grade but focussed on the outcomes specified in the GRADE analysis

			dolutegravir group (36/242 [15%]) than in the darunavir plus ritonavir group (21/242 [9%]), as in the analysis at 48 weeks. In the dolutegravir group, three serious adverse events (tendon rupture, polyarthritis [both after 48 weeks], and suicide attempt) were deemed possibly drug related; none in the darunavir plus ritonavir group were classed as drug related. Reference: Molina, J.M., Clotet, B., van Lunzen, J., Lazzarin, A., Cavassini, M., Henry, K., Kulagin, V., Givens, N., de Oliveira, C.F., Brennan, C. and FLAMINGO Study Team, 2015. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. The lancet HIV, 2(4), pp.e127-e136. Thank you for your consideration	
	Sophie Ross	Clinic-T, Brighton Sexual Health, University Hospitals Sussex NHS Foundation Trust	Thank you for the opportunity to review the consultation draft of these guidelines. We would like to make a few comments in relation to Section 8.9 relating to transgender people. At the introduction to this section you have explained gender reassignment to be a protected characteristic under The Equality Act (2010) and used the definition as contained in the Act. It has been clarified, however that the use of 'gender reassignment' in this context applies to all transgender people, not just those undertaking medical transition, as per the explanatory notes for The Act, is it worth stating this explicitly? (https://www.legislation.gov.uk/ukpga/2010/15/notes/division/3/2/1/4) With regards to section 8.9.1, you have recommended that registration forms and electronic records record both gender and sex assigned at birth. However the LGBT foundation produced a good practice guide for monitoring sexual orientation and gender in healthcare in which they recommended that the question be asked as follows. Part 1: Which of the following options best describes how you think of yourself? 1. Woman [including trans woman] 2. Man [including trans man] 3. Non-binary 4. In another way (and an option to decline to answer). Part 2: Is your gender identity the same as the gender you were assigned at birth? 1. Yes 2. No (and an option to decline to answer). This ensures that accurate information on gender is collected in a sensitive way. Of note it does not ask the person to state the sex that they were assigned at birth, and it is difficult to justify why this information would be required for clinical practice, over and above the knowledge that the person's gender now is not the same as they were	Thank you - we have amended the sentence related to The Equality Act accordingly Thank you - we are somewhat limited by the typical classification within electronic patient records. We will consider this in more detail in the BHIVA monitoring guidelines and have amended these guidelines to better reflect this suggestion

			assigned at birth. Moreover, it may be traumatic and triggering of dysphoria to require transgender people to disclose this information. As a protected characteristic under The Equality Act (2010), it is imperative that information on gender diversity is treated in strict confidence, and disclosure of such information is only made where necessary for clinical care, or this could be seen as a breach of the Gender Recognition Act (2004). Of note BASHH have adopted the LGBT foundation recommendations in their recommendations on integrated sexual health services for trans people. Section 8.9.4 concerns drug-drug interactions between ART and hormonal treatment, which you rightly state is a common concern amongst transgender people living with HIV, and may present a barrier to accessing ART. Although it is important to note there are some clinically significant interactions, we feel it is important that clinicians reassure patients taking, or hoping to take GAHT that ART can and will be tailored to avoid or manage interactions, to dispel the common fear that GAHT will be stopped if interacting with HIV treatment, and encourage open discussion about self medicating with hormones, a practice that is common but rarely disclosed to healthcare professionals (Nambiar et al, 2018). Thank you!	Thank you - we have added a sentence
	Gilead Sciences		Thank you for the opportunity to review this welcome update to the HIV-1 Treatment Guidelines, and congratulations to the Committee for updating them during these particularly challenging times. Note that for ease of Committee review, these comments have been listed in section order, rather than based on the priorities of Gilead. We have tried to limit comments to sections in which Gilead products are discussed, or where there are differences in the level of detail provided for comparator vs Gilead regimens. We have repeated some comments where similar topics are raised across different sections (e.g weight or lipids), and cross referred to other sections for ease of committee review. Page numbers cited refer to the fully reference consultation version We ask that any publicly disclosed comments are attributed to Gilead Sciences, rather than any named individual. Thank you to the Committee for considering our comments. **1.2.1 Guideline development process** The data search window included abstracts up to September 2019 and publications up to February/March 2020. We are assuming this is for the analyses	Thank you Thank you for listing your comments in order of section as opposed to the priorities of Gilead Thank you We have removed the submitting individual's name

			of the BHIVA PICO questions only (appendix 2), given the presence of publications in some sections after these dates, including but not limited to the SALSA study which has been appropriately referenced in a number of sections. **5.2.2 Dolutegravir versus bictegravir (page 34)** • We note the relative brevity of detail provided for this drug comparison compared to other comparisons, including the lack of some outcomes which, although not Committee defined critical outcomes, are included in other comparisons. We suggest that all comparisons of recommended regimens be discussed with similar levels of detail. • Virologic outcomes: o We suggest that similarly detailed descriptions of outcomes and durations of follow-up be provided for the 1489 and 1490 studies, as per other comparisons. o The committee states '*no resistance was detected in any arm* [till W96]' but we do note that two participants within the 1489 study taking DTG/ABC/3TC developed treatment emergent resistance with M184V mutation during the randomised phase (W144 to unblinding, Pozniak A, et al. EACS 2021, Poster PE2/68). • Drug-related adverse events (DRAE): o Fewer participants on BIC/FTC/TAF experienced DRAEs vs DTG/ABC/3TC and DTG+FTC/TAF, but this is not outlined in the overview, whereas similar differences are discussed for other regimens (e.g. 5.2.3 dolutegravir/lamivudine). o Within study 1489 at week 96 (BIC/FTC/TAF vs DTG/ABC/3TC), participants in the BIC/FTC/TAF group had a lower incidence of DRAEs than those in the DTG/ABC/3TC group (89 [28%] of 314 vs 127 [40%] of 315, p=0.02) (Wohl DA et al. Lancet 2019;6:e355-e363). o Within study 1490 (BIC/FTC/TAF vs DTG+FTC/TAF) DRAEs were significantly lower at 64 (20%) vs 92 (28%) at W96 for BIC/FTC/TAF vs DTG+FTC/TAF, respectively (p=0.02) (Stellbrink HJ et al. Lancet 2019;6:e364-e372). Both 1489 and 1490 studies had similar and low rates of discontinuation due to any adverse events between arms. • Regarding quality-of-life measures, we also note that BIC/FTC/TAF was associated with a lower prevalence of some bothersome symptoms than DTG/ABC/3TC at 48 weeks using validated patient reported outcome measures (1489 study, ART naive): In treatment-naïve adults, fatigue/loss of energy, nausea/vomiting, dizzy/light headedness, and difficulty sleeping were reported significantly less with B/F/TAF at two or more time points. Fatigue	Thank you - the dates reflected an older version and have been updated accordingly Thank you. We have added further detail regarding virological success outcomes and clarified timepoints We will clarify that resistance at failure was up to week 96. Longer periods of follow-up were not identified in the selected clinical outcomes for the GRADE analysis The following adverse event outcomes were identified by the writing group in the clinical outcomes ranked as critical or important: 1) Adverse event-driven discontinuation 2) Serious adverse events 3) Drug-related serious adverse events 4) Grade 3 and 4 adverse events 5) Drug-related grade 3 and 4 adverse events We have amended the text to ensure consistency in adverse events discussion in all sections. Recommendations follow the identified critical/important outcomes

			and nausea were also significantly less common for those receiving B/F/TAF in longitudinal models. Additionally, in virologically suppressed participants, nausea/vomiting, sad/down/depressed, nervous/anxious, and poor sleep quality (from the PSQI) were reported significantly less with B/F/TAF than DTG/ABC/3TC at two or more time points, as well as in longitudinal models. (Wohl et al. Patient 2018;5:561-573) • We therefore suggest the committee provide and describe the data for DRAEs for BIC/FTC/TAF vs DTG+F/TAF and DTG/ABC/3TC as they have with other comparisons, and provide virologic outcome data for the 1489 and 1490 studies consistent with level of detail included for other regimens. **5.3.5 Tenofovir-DF/emtricitabine compared with tenofovir-AF/emtricitabine (page 38)** • We suggest the committee describe the number of participants developing proximal renal tubulopathy (PRT) within an integrated analysis of 26 Phase 2/3 clinical trials (N=9,322) representing exposures totalling 12,519 person-years (py) on TAF and 5,947 py on TDF (Gupta et al. AIDS 2019;33:1455-65): ○ PRT: 0 cases with TAF, 10 cases with TDF (p<0.001) • The Committee cites a metanalysis by Hill *et al* which it states "*suggested that these differences in renal and bone markers are not seen in the absence of the pharmacokinetic boosters cobicistat and ritonavir*", however we believe this is an inaccurate summary of this publication: ○ Regarding BMD, the publication outlines statistically significant differences in BMD between TAF and TDF for boosted vs unboosted comparisons, with Hill et al stating "*The test for differences by boosting revealed considerable heterogeneity between subgroups for percentage change in hip BMD at 48 weeks (I2=75.8%). In the subgroup of studies where TAF was compared with boosted TDF, percentage decreases in hip BMD were 1.98% smaller in TAF than in TDF (95% CI 1.63% to 2.34%, P<0.001), whereas in unboosted TDF regimens this mean difference reduced to 1.48% (95% CI 1.14% to 1.81%, P<0.001). Differences were also observed between boosted and unboosted subgroups for spine BMD (I2=51.4%). TAF was associated with a 2.11% (95% CI 1.80% to 2.41%, P<0.001) smaller percentage decrease in spine BMD than boosted TDF whereas this mean difference reduced to 1.73% (95% CI 1.32% to 2.14%, P<0.001) when TAF was compared with unboosted TDF*".	We acknowledge that quality of life measures are important. However, these are not consistently measured and reported across studies, so are not a critical endpoint at present. We aim to compare these issues indirectly through adverse event outcomes Drug-related adverse events overall were not considered a critical outcome Thank you. Proximal renal tubulopathy occurs in about 0.4% of individuals receiving a TDF-containing regimen. This is covered in section 8.4.1. We chose to consider phase 3, not 2, data for the guidelines Thank you. We agree that differences in BMD and renal biomarkers are also observed in individuals who switch from TDF to TAF as part of unboosted regimens (Hagins, HIV Med 2018; 19: 724-733). Reference to the meta-analysis by Hill et al has been removed from section 5.3.5

			○ Regarding renal biomarkers, we note that only discontinuations due to renal AEs were reported by Hill et al, rather than any biomarkers such as proteinuria or CrCL. • We also suggest that differences in BMD and eGFR with TDF vs TAF "*are not seen in the absence of the pharmacokinetic boosters cobicistat and ritonavir'"* might be to ignore the data for renal events, including PRT, in people taking TDF using unboosted regimens within well-defined cohorts, or other studies, including but not limited to: ○ Within the DISCOVER study (FTC/TAF vs FTC/TDF for men who have sex with men and transgender women at risk for HIV), FTC/TAF was associated with more favourable changes in $eGFR_{CG}$, β2M:Cr, and RBP:Cr compared with FTC/TDF. Treatment-emergent proteinuria was more common with FTC/TDF than FTC/TAF (24.3% vs. 21.3% P = 0.009), as were treatment-emergent elevations in UPCR >200 mg/g (35 [1.5%] vs. 16 [0.7%], P = 0.005). Compared with FTC/TDF, participants taking FTC/TAF had numerically fewer study drug-related renal AEs, severe study drug-related renal AEs, and discontinuations due to renal AEs. PRT (Fanconi syndrome) was reported in one participant in the FTC/TDF arm and none in the FTC/TAF arm. (Mills et al. Open Forum Infect Dis. 2019;(Suppl 2): S64.) • Regarding the committee's comment about renal biomarker improvement and "*lack of data as to whether the same applies to first-line ART*," we note that within the GS-104/111 studies there were significantly fewer renal-related discontinuations for those on EVG/COBI/FTC/TAF vs EVG/COBI/FTC/TAF (0 vs 12, P<0.001), and 0 vs 4 cases of PRT respectively out to 144 weeks (Arribas J, et al. JAIDS 2017;75:211-8.) **5.6 What to start in the context of rapid ART initiation (page 43)** • We note that the committee commented to lack of published data on rapid ART initiation with BIC/FTC/TAF. We would draw the Committee's attention to the FAST study of 112 ART-naive participants initiating BIC/FTC/TAF (Bachelard A, et al. EACS 2021, Poster PE2/7). Although this was presented outside the publication window, we note that the Committee included the STAT study, with week 24 primary outcomes presented in August 2020 (Rolle CP et al. 14th annual American Conference for the Treatment of HIV; August 20-22, 2020; Virtual) **5.10.1 NRTI switch (page 48)**	DISCOVER is a study of PrEP and not HIV treatment and was therefore not considered Thank you. We agree and this statement has been removed from section 5.3.5 Thank you - added

			• We note our overlap of comments between this section and 8.3.2 (lipid considerations) and 8.3.3 (weight gain considerations)
			• Regarding Lipids:
			  ○ The Committee comments on "*slight worsening of lipid parameters*" when switching from TDF to TAF. We note that while worsening usually refers to the increase in Total and LDL cholesterol, this is accompanied by an increase in HDL with no clinically meaningful change in TC:HDL ratio.
			  ○ We note that within HIV negative populations FTC/TAF has shown a lipid-neutral effect, while FTC/TDF has shown a mixed effect on lipid fractions:
			  ▪ Lipid fractions at Week 96 within the DISCOVER study (FTC/TAF vs FTC/TDF for pre-exposure prophylaxis) (Ogbuagu O. et al, CROI 2020, Boston, MA. Oral 2940)
			  • TC: -0.08 vs –0.36 mmol/L (P<0.001)
			  • LDL: -0.05 vs –0.18 mmol/l (p=0.001)
			  • HDL: -0.03 vs –0.10 mmol/l (p<0.001)
			  • Triglycerides: +0.03 vs -0.05 mmol/l (p<0.001)
			  • TC:HDL ratio: +0.1 (Baseline 3.4) vs 0 (BL 3.5)
			  ○ This effect is likely to be related to TDF rather than TAF, as similar changes have been observed in comparisons of TDF vs. other NRTIs or RAL in both switch and ART naïve populations
			  ▪ ART naïve:
			  • GEMINI: DTG/3TC vs DTG+FTC/TDF (Cahn P et al. Lancet. 2019; 393:143-55)
			  • NEAT 001/ANRS: ART naive DRV/r+RAL vs DRV/r+FTC/TDF (Bernardino JI. Lancet HIV. 2015; 11:e464-73)
			  ▪ Virological suppressed switch:
			  • SWIFT: Switch to PI/r+FTC/TDF or remain on PI/r+ABC/3TC where participants who switched to FTC/TDF showed greater reductions from baseline at week 48 in fasting TC (median change of −21 mg/dL vs −3 mg/dL with 3TC/ABC, P < .001), and LDL (−7 mg/dL vs 2 mg/dL with 3TC/ABC; P = .007) (Campo R. Clin Infect Dis. 2013; 11:1637-45)
			  • GS-US-311-1717: Switch from ABC/3TC to FTC/TAF was not associated with significant differences in fasting total cholesterol, LDL cholesterol, and
				Thank you - clarification added
				
				Thank you but considering that lipids are not a critical endpoint we have kept discussion brief. We have emphasised that there are no data regarding CVD risk related to lipid changes

			triglycerides at week 48. Changes in HDL cholesterol were significantly different, but were not considered clinically relevant. There were no differences between groups in changes in TC:HDL ratio. (Winston A et al. Lancet HIV 2018; 5:e162-71) ○ Gilead therefore suggest the Committee provides greater clarity on the relevance of the observed lipid changes with TDF to TAF switches, and contextualise this with similarity of outcomes for other non-TDF comparators. • Regarding weight, we believe the Committee may have overemphasised any role of TAF in weight change, given the increasing evidence that weight change with TAF-based regimens is no different from that observed with non-tenofovir-based regimens such as DTG/3TC. ○ There is growing consensus that it is the comparison of regimens that contain weight suppressive agents (most notably TDF and EFV) versus those that do not have appreciable weight suppressive effect that drives weight differences among ART regimens: ▪ A meta-analysis of randomised control trials comparing FTC/TDF or TDF (n=9,444) to control (placebo or cabotegravir, n=6,691) in HIV-negative individuals reported that individuals taking TDF where more likely to observe a 5% weight loss or report ≥ Grade 2 abnormal loss of weight compared to controls (odds ratio 1.44 95% CI 1.12 – 1.85 p = 0.005) (Shah S, et al. ID Week 2021, 882) ▪ TDF-based regimens have shown a weight suppressive effect vs DTG/3TC in the GEMINI studies (DTG/3TC vs DTG+FTC/TDF), with less weight gain observed on DTG+FTC/TDF (mean 2.1 kg) vs DTG/3TC (3.1 kg) in ART-naive populations at week 96 (Cahn P et al. JAIDS 2020;83:310-318). ▪ The randomised TANGO study showed that staying on a TAF-based regimen had a similar weight trajectory vs switching off TAF to DTG/3TC at week 48 and through 144 weeks. There were also no differences in the percent with outlier weight gain. • At week 48 for DTG/3TC vs remaining on TAF, respectively (Wyk J, et al. AIDS 2020. Oral OAB0606; van Wyk et al. Clin Infect Dis 2020):	Thank you. We agree and have modified the text in section 5.10.1 as follows: Most reported changes are likely to have resulted from the removal of the weight-restricting properties of the high tenofovir exposures achieved with tenofovir DF.

			• Similar overall weight change: +0.81 vs +0.76 kg • Similar change when compared to boosted TAF regimens: +0.81 vs +0.88 kg • Similar change when compared to unboosted TAF regimens (mainly DTG- or RPV-based): +0.81 vs +0.40 kg • Similar weight gain of ≥10%: 3 vs 4% • Through 144 weeks the weight changes were similar when remaining on TAF (+1.7 kg) vs switch to DTG/3TG (+2.2kg) (van Wyk J, et al. vIAS 2021, PEB164). ▪ The SALSA study (switch to DTG/3TC) is the first demonstration that stopping TDF rather than switching to TAF is clearly associated with weight gain, which is consistent with the known TDF weight suppressive effect cited above. Weight gain at week 48 for those taking DTG/3TC was greater when switching from TDF-based ART vs remaining on TDF (difference +2.4kg, 95% CI 1.2, 3.6), but no different when switching vs remaining on TAF-based ART (+0.2 kg, 95% CI -1.2, 1.5) (Hagins D, et al. CROI 2022, Poster 603). **5.10.4 Integrase switch (page 52)** ▪ The text states: "*The majority of TANGO participants (around 75%) were on coformulated tenofovir-DF/emtricitabine/elvitegravir/cobicistat at baseline,"* but in fact the majority were on tenofovir-AF/emtricitabine/elvitegravir/cobicistat. ▪ The Committee mentions the increase in weight in 4030 study: "*the only notable difference was greater weight gain in those switching from tenofovir-DF to tenofovir-AF compared to those already on tenofovir-AF at baseline."* For balance we suggest that the committee also note the lack of difference in weight change with switch from TAF-based ART to DTG/3TC in TANGO at week 48 irrespective of boosting, (Wyk J, et al. AIDS 2020. Oral OAB0606; van Wyk et al. Clin Infect Dis 2020) and through W144 (van Wyk J, et al. vIAS 2021, PEB164). Additionally, the greater increase in weight within SALSA in those switching from TDF-based ART to DTG/3TC (difference in adjusted mean change at week 48 +2.4 kg, 95% CI 1.2, 3.6), with no difference in those	Thank you for spotting this error - it has been corrected Thank you - added

			switching from TAF (+0.2 kg, 95% CI -1.2, 1.5) (Hagins D, et al. CROI 2022, Poster 603). **5.11.1.1 Dolutegravir with lamivudine** • We suggest for balance the committee outlines weight changes observed with switch to DTG/3TC within the TANGO (vs continuing TAF-based regimen, Wyk J, et al. AIDS 2020. Oral OAB0606) and SALSA studies (vs continuing TDF- or TAF-based regimens, Hagins D, et al. CROI 2022, Poster 603) studies.	Added already (see above point)
			5.2.3 Dolutegravir/Lamivudine (page 34) • We note the statement that '*Drug-related adverse events in the pooled analysis were numerically more common in the three-drug regimen arm (24% vs 18%)*' however: ○ We note this was not a defined critical outcome within the prioritised clinical outcomes in *5.1 Introduction.* ○ We suggest clarification are provided as to which grade DRAEs are being reported, noting that within the publication it states 6% and 7% of participants reported grade 2-5 DRAEs for DTG/3TC and DTG-FTC/TDF respectively, vs 18% and 24% respectively reporting all-grade DRAEs (Cahn et al, Lancet 2019; 393,143-155, Table 5). This suggests the majority were grade 1 DRAEs. ○ We suggest the Committee avoid overgeneralisation of this and other outcomes to two-drug and three drug regimens, but specify that it applies to DTG/3TC and DTG+FTC/TDF, given the lack of current data comparing DTG/3TC to other regimens in ART-naïve populations. • The Committee states that no emergent resistance was observed in RCTs for DTG/3TC through week 96; however, a case was observed by W144 (Cahn et al. HIV Glasgow 2020, Poster 018). Although outside of the publication window, we suggest this is important to contextualise the known data for this regimen. **5.3.1 Doravirine (page 35)** • For consistency with other regimens, we suggest that the committee outline the critical outcome of '*Proportion developing resistance at virological failure'* for doravirine, which has shown similar levels of NRTI resistance at virologic failure to that observed with EFV/FTC/TDF at week 48, with fewer NNRTI RAMs (Orkin C et al. Clin Infect Dis. 2019;68:535-44).	Thank you, we agree and have removed this point, summarising only the adverse event endpoints that are also considered critical outcomes We do not include week 144 analyses in this guideline. A single VF after week 96 would not alter our recommendations Thank you - added

			6.1.3.1 Effect of adherence on virological suppression ○ Regarding adherence and the 1489 and 1490 studies, the Committee states that "*Although differences were not statistically significant between study arms for either study, the numerical differences between the adherence strata for individual regimens indicate that adherence influences outcomes for these high-genetic barrier INSTI-based regimens."* We have concerns about the interpretation of this statement, and the differences in interpretation of other similar data, noting ○ The P-values for difference between treatment arms at <95% adherence are P=0.65 for 1489 study, and P=0.35 for 1490. These P values likely reflect the relatively small numbers of participants within these groups ○ We also note that not all of those who are not 'successes' (VL<50c/ml on assigned treatment arm) would necessarily be failures (VL>50c/ml). Discontinuation from study drug for other reasons or withdrawal from the study for administrative reasons would need to be considered before any clinical interpretation of trends. ○ We suggest these factors may leave the potential for the audience to overinterpret the Committee's statement that '*the numerical differences between the adherence strata for individual regimens indicate that adherence influences outcomes for these high-genetic barrier INSTI-based*'. ○ Within the GEMINI studies, the Committee states that those with <90% adherence achieved viral suppression "to a similar degree." Cahn et al report the proportion of participants with HIV-1 RNA <50 copies/mL (Snapshot) at Week 48 in the <90% adherence group was 69% in the DTG+3TC group and 65% in the DTG+FTC/TDF group. We note that this 4% difference in outcome with <90% adherence (in 5% of all study participants) are described as "*a similar degree*," whilst for BIC vs DTG a 5-6% difference with high P-value, and numerically higher rates of viral suppression (noting for <95% adherence) are described as a '*numerical differences*' which we suggest are not consistent interpretation of these small analyses. ○ We note that no emergent resistance has been observed for any participants inconsistently taking BIC/FTC/TAF within 1489 or 1490 out to W240 (Wohl et al. CROI 2022) or DTG-FTC/TAF within 1490 till W144 (Orkin C et al. Lancet HIV. 2020;6:e389-e400).	Thank you - we accept that the wording may have caused confusion so have rephrased, removing 'numerical difference' to: 'Differences in viral suppression by adherence were not statistically significant between study arms for either study [2,55], but lower virological success rates between the adherence strata for individual regimens indicate that adherence rates influences outcomes for these high-genetic barrier INSTI-based regimens, as would be expected' We have added a point of clarity related to VS versus VF As above We have retained 'to a similar degree' as the concern here would be that 2DR underperform to a greater degree, and as your comment highlights, the opposite was true. We do not wish to overinterpret the fact that 3DR underperformed slightly more at lower adherence so have kept the phrasing unchanged. We note we provided much more detail for GS-1489 and -1490 than we did for GEMINI so, considering the limitations of these analyses, we have reduced the level of detail in line with the GEMINI description We agree and have added this for GS-1489 and -1490 as well as GEMINI for weeks 48 and 96

			○ For DTG/ABC/3TC, we note within the 1489 study that two cases of emergent resistance have been observed, both with M184V (Pozniak A, et al. EACS 2021, Poster PE2/68) ○ We also note the case of emergent resistance within the GEMINI studies for a participant inconsistently taking 3TC+DTG with M184V at Week 132 and added R263R/K at Week 144 (Orkin C et al. CROI 2021)	After the week 96 timepoint which we do not consider for these guidelines As above
			.3.4 First-line treatment failure with first- and second-generation INSTI-based resistance (page 90) ○ The Committees states that *"resistance is extremely rare in studies in treatment-naïve individuals with dolutegravir or bictegravir/two-NRTI-based regimens.*" However, no emergent resistance to BIC/FTC/TAF, or DTG+FTC/TAF has been observed in either 1489 or 1490 studies within the randomised phase out to W144 (Orkin C et al. EACS 2019) or the open-label extension out to Week 240 for BIC/FTC/TAF (Wohl D et al, CROI 2022). Two cases of emergent M184V were observed for participants taking DTG/ABC/3TC within the randomised phase of the 1489 study (Pozniak A, et al. EACS 2021, Poster PE2/68)	The statement remains true, even on DTG/ABC/3TC resistance is rare, but we have added 'two cases' to the text.
			7.5 Individuals with limited or no therapeutic options when a fully viral suppressive regimen cannot be constructed (page 96) • The Committee states that *'The favourable pharmacokinetic properties of lenacapavir allow for potential oral single dosing over 6 months, although subcutaneous injection was used in the trial.'* • Please note that only the long-acting injection is being developed for 6 monthly dosing intervals. The long-acting oral formulation is under evaluation for daily and weekly administration.	Thank you - corrected
			8.1.4 Simplification strategies (page 016) ▪ The Committee suggests "*Novel ARV strategies, particularly dual therapy with INSTIs or PIs, continue to be of interest given the potential for reduced long-term toxicities."* Gilead notes while there is a potential for differential longer term toxicity, randomised studies comparing continued TAF vs stopping TAF and using DTG/3TC have not shown any reduction in toxicity with 144 weeks follow up (TANGO, Osiyemi O et al. CID 2022, doi: 10.1093/cid/ciac036. Online ahead of print). It is speculative and remains	Considering this statement precedes a discussion about the limitations of 2DR we do not think an amendment is necessary. Importantly the statement uses *potential* reduction in long-term toxicity to explain the interest in 2DR. We do state that there is evidence to support this

			uncertain what longer term follow up might show in terms of longer term toxicity. **8.2.1 What to start (CKD) (page 112)** ▪ The Committee states, "*The relative safety of tenofovir-AF has also been demonstrated in individuals with CKD (eGFR 30–70 mL/min/1.73 m^2), with marked reductions in tubular proteinuria within days of switching from tenofovir-DF to tenofovir-AF, and stable eGFR over 96 week*s." We note that these data have been extended to 144 weeks of follow up (Podzamczer D, et al. IAS 2017, Paris. Poster #MOPEB0288) with no reported proximal renal tubulopathies and few (5) renal-related discontinuations from 242 enrolled participants. We note that this has been highlighted in *8.2.2 Need to switch*. **8.2.2 Need to switch (page 112)** ▪ We suggest the Committee highlight the results of the FANTA study, in which individuals with a history of PRT on TDF were switched to TAF. After 96 weeks of TAF exposure, there was no recurrent PRT or adverse effects on biomarkers of proximal tubular function. This study is referenced but not discussed. **8.2.3 Dose adjustment of ART in the setting of renal impairment (page 114)** ▪ We suggest the Committee clarifies which eGFR strata and what data there are to support '*Intermittent dosing is well established for tenofovir-DF [34]*' noting that the supporting reference (Yombi et a.l HIV Med 2015; 16: 457–467.) does not appear to provide data suggesting safety is well established beyond dosing guidance. **8.3.2 Lipid considerations (page 118)** ▪ We note our overlap of comments between this section and 5.10.1 (NRTI switch) and kindly refer the Committee to our comments on lipids made within 5.10.1 ▪ We suggest the committee broaden the groups in the following statement to include DTG/3TC, noting the GEMINI study shows similar outcomes: "*Conversely, the NRTI tenofovir-DF was associated with beneficial effects on overall lipid profiles in healthy volunteer studies [7], when used for PrEP [8] and compared to the NRTIs abacavir [9] and tenofovir-AF [10] in randomised*	Thank you – there are no randomised studies of initiating ART in people with CKD/eGFR <60 that can inform this question Thank you - we have amended as follows: 'Tenofovir AF had no effect on tubular biomarkers or BMD in a prospective study of individuals with a history of proximal tubulopathy on tenofovir DF, and no recurrent cases of proximal tubulopathy were observed over 96 weeks' Thank you. We have added the threshold of 50 mL/min/1.73 m^2 Thank you. We have clarified that a switch from tenofovir DF to tenofovir AF was associated with a slight deterioration in some lipid parameters. The committee remains unconvinced that these small changes merit detailed discussion in these guidelines

			trials". We suggest for context and balance these data be described for DTG+TDF/FTC vs DTG/3TC in ART-naïve populations within the rationale (Cahn P et al. Lancet 2019;393:143-55), as they show similar trends to TDF vs TAF comparisons. ▪ Regarding the Committee's statement that "*Switch from tenofovir-DF to tenofovir-AF was associated with a deterioration in lipid parameters*", We also refer the Committee to our comments on lipids from section 5.10.1 NRTI switch, including those within HIV negative populations where FTC/TAF has shown a lipid-neutral effect, while FTC/TDF has shown a mixed effect on lipid fractions ○ Lipid fractions at Week 96 of the DISCOVER study (FTC/TAF vs FTC/TDF for pre-exposure prophylaxis) (Ogbuagu O. et al, CROI 2020, Boston, MA. Oral 2940) ▪ TC: -0.08 vs –0.36 mmol/L (P<0.001) ▪ LDL: -0.05 vs –0.18 mmol/l (p=0.001) ▪ HDL: -0.03 vs –0.10 mmol/l (p<0.001) ▪ Triglycerides: +0.03 vs -0.05 mmol/l (p<0.001) ▪ TC:HDL ratio: +0.1 (Baseline 3.4) vs 0 (BL 3.5)	
			8.3.3 Weight gain considerations (page 118) ▪ We note our overlap of comments between this section and 5.10.1 (NRTI switch), and also kindly refer the committee to comments on weight made within 5.10.1. ▪ We suggest that the "*ARV drugs [which have been] associated with greater weight gain versus comparator agents*" be expanded to include DTG/3TC vs DTG+FTC/TDF given the data from the GEMINI studies, further supported by TANGO and SALSA studies. ▪ Within GEMINI, ART naïve participants taking DTG/3TC gained 3.1 kg vs 2.1 kg for DTG+FTC/TDF at W96 (Cahn P et al. JAIDS 2020;83:310-318). ▪ We also note that weight change were similar when switching from TAF-based regimen to 3TC/DTG (TANGO) at week 48 irrespective of switch from boosted or unboosted TAF-based regimen (Wyk J, et al. AIDS 2020. Oral OAB0606, see comments on section 5.10.1 for further detail), with no difference in weight gain in overall analysis at week 144 (van Wyk et al IAS, 2021, PEB164), supporting the similar profile of DTG/3TC and TAF-based regimens. ▪ The committee comments that '*Tenofovir-AF has also been associated with greater weight gain when compared to tenofovir-DF in first-line studies, most markedly in black women*', citing the ADVANCE study. We note that within	Thank you for these comments. At the time of writing, and the limited data we have on weight changes with different antiretroviral therapies, our section on weight gain summarises current considerations. As data evolve, we envisage future iterations of the guidelines will include further details

			the ADVANCE study, the BMI of both women and men on DTG+FTC/TAF returned to the societal norm of the general South African population by week 144 of the study. ○ BMI from the ADVANCE study for participants randomised to DTG+FTC/TAF vs WHO data on 2016 South African population BMI (Carr A. Glasgow 2020 via https://www.hivglasgow.org/2020-webcast, accessed June 2022): ▪ Women: 30.1 vs 29.2 kg/m^2, ▪ Men: 24.2 vs 24.7 kg/m^2. ○ This is consistent with TDF having a weight suppressive effect and therefore lesser weight gain within the DTG-FTC/TDF vs the DTG+FTC/TAF arm. ▪ The Committee suggests that weight differences between TDF and TAF '*may, in part, be explained by the abrogation of weight loss observed on tenofovir-DF, best demonstrated in PrEP trials [24], though this is non-progressive and typically less than 1 kg*'. We suggest that the OPERA study further supports this non-progressive change given that the increase in weight with the switch from TDF to TAF occurred mainly in the first 9 months, followed by a return to the pre-switch weight trajectory (Mallon et al JAIDS 2021; 24: e25702) ▪ We agree with the statement that *'There is no evidence at present to support switching ART to manage weight gain,'* but in addition to the ongoing or planned trials, we note that the TANGO and SALSA studies clearly demonstrate that switch from TAF-based regimens to DTG/3TC has no impact on weight trajectory. Switch from TDF to DTG/3TC within SALSA results in weight increase based on the removal of the TDF weight suppressive effect (Hagins D, et al. CROI 2022, Poster 603). These studies provide strong evidence that discontinuation of TAF is not an effective approach to ART-associated weight increase.	
			8.4.2.1 Efficacy (women) (page 121) ▪ Gilead would highlight two studies assessing safety and efficacy of TAF-based ART in women living with HIV: ○ Hodder et al (J AIDS 2018; 78: 209–13.) reported that switching to EVG/COBI/FTC/TAF in an RCT was non-inferior to continuing ATV + RTV + FTC/TDF for the outcome of HIV–1 RNA <50 cps/ml at week 48. ○ The 1961 study of switch of ART to BIC/FTC/TAF in women with HIV on stable suppressive ART regimen with randomised follow up (vs remaining on current ART) until W48 (Kityo C, et al. JAIDS	Thank you - we have added the data from Hodder et al

			2019;82:321–8) and ongoing follow-up on those on BIC/FTC/TAF through W96 (Kityo C, et al. IAS 2019, #MOAB0106). These data demonstrated non-inferior efficacy at W48 followed by ongoing maintenance of viral suppression through W96. **8.5 Mental health (page 127)** ▪ We are concerned about the statement that '*We recommend that INSTI-containing regimens should be used with caution in patients with a pre-existing history of any psychiatric illness including depression (GPP)*.' ○ The Committee points to the raltegravir SmPC caution with pre-existing history of psychiatric illness; however, this is not stated in the SmPCs of elvitegravir (as EVG/COBI/FTC/TAF), BIC (as BIC/FTC/TAF) or DTG. ○ In STARTMRK, RAL was associated with fewer nervous system and some psychiatric disorders (abnormal dreams) vs EFV. ○ We also note that there were fewer of some neuropsychiatric AEs with DOR vs EFV in ART naïve studies, and that there were numerically similar and low proportions reporting depression and suicide/self-injury (4.1% vs 6.6% DOR vs EFV, W48) and psychosis and psychiatric disorders (0.3 vs 1.1% Week 48) (Orkin C. Clin Infect Dis. 2019; 68:535-44). We do note however there are no data comparing the safety of DOR to any INSTI; therefore, the impact of DOR on those with mental health challenges is not well understood. ○ Although the Committee contextualised this recommendation noting that INSTIs have outperformed other ARV classes, we believe further detail and substantiation of the data are required before class generalisations are appropriate. **8.7.1 What to start (bone health) & 8.7.2 Switching treatment (page 136)** • The Committee recommend against the use of TDF in those with '*FRAX score of >10% (major osteoporotic fracture)'*. We suggest the Committee provide guidance on how HIV infection should be considered a secondary risk factor for osteoporosis with FRAX calculations. This would align with EACS guidelines (version 11.0, October 2021) and NHS-E TAF policy guidance. **8.8.33 What to start (later life) (page 141)** • We suggest that the Committee provide a recommendation against the use of TDF-based ART in older persons with HIV, either as a graded or GPP, given	Thank you for this comment. Given that the SmPC for raltegravir includes this caution, and that neuropsychiatric side effects have been reported with the INSTI class of antiretroviral therapy, the writing committee considers this caution should remain Thank you - this is the remit of the monitoring guidelines, we will pass this comment to that writing committee Thank you for this comment. The later life section summarises some recommendations for treating older individuals living with HIV. Given that

			the availability of other strategies without notable renal or bone adverse events, since these comorbidities are more prevalent in this population. • We also suggest that the Committee outline what existing safety data in older individuals has been presented, which could include: ○ Pooled analysis of 140 participants ≥65 years old from 4 international trials of virologically suppressed participants taking BIC/FTC/TAF (Ramgopal M, et al. AIDS 2020. Oral OAB0403), which includes study 4449, which specifically recruited from this population, and includes 96-week data (Maggiolo F, et al. vIAS 2021, PEB160). ○ The GS112 study in those with CrCl 30-70 ml/min who received EVG/C/FTC/TAF, where the median age was 59 years, with over 20% >65 years with follow-up through 144 weeks (Podzamczer D, et al. IAS 2017, Paris, France. Poster #MOPEB0288). ○ An age analysis (≥ 50 years [n=196] vs <50 years [n=1078]) of the 1489 and 1490 studies supporting the use of BIC/FTC/TAF with DTG+FTC/TAF and DTG/ABC/3TC in this population (Mills A, et al. CROI 2020, #477.) We again wish to thank and congratulated the Committee on these guidelines, and for the opportunity to provide comment.	toxicities with TDF are covered in other sections (bone and renal), we do not consider a specific recommendation is warranted in this section Thank you
	Andrew Murungi	ViiV Healthcare UK	ViiV Healthcare UK commend the BHIVA ARV Treatment Writing Group on a comprehensive set of guidelines for the treatment of adults living with HIV-1. We also welcome the opportunity to participate in the consultation process for the guidelines. Please see below for comments: Table 5.1 Recommendations for choice of first-line ART: The table summarising the first-line ARVs 'Recommended as initial treatment for most people living with HIV (Grade 1A)' includes caveats for Dolutegravir/lamivudine which we will comment on in points below. Section 5.2.3 Dolutegravir/lamivudine In the summary of this section, several caveats are listed for dolutegravir/lamivudine. The term not suitable (with 'not' in bold) is used to list the caveats. The use of this term (not suitable) is only used in this section and not in other parts of the guidelines where 'Not recommended' is the phrase most used. This inconsistency may imply the Treatment Writing Group feel more strongly on these caveats. We request a consistency of phrasing with 'not	Thank you Thank you - amended to 'not recommended' instead of 'not suitable'

			suitable' replaced with 'not recommended. However, if the Writing Group feel not suitable is more appropriate for these caveats, could they please provide clarity why this stronger emphasis is being made. 1. It is not suitable for those with pre-treatment viral load >500,000 copies/mL "People with a pre-treatment viral load >500,000 copies/mL were excluded…. The viral load exclusion may limit the generalisability of the findings, although a small number of individuals did have a viral load >500,000 copies/mL at the baseline visit. The proportion of people with viral loads >500,000 copies/mL in recent clinical trials is generally small. For example, in the ADVANCE study where participants had relatively advanced HIV with a median CD4 count In the current draft guidelines, the Writing Group acknowledge the proportion of people with viral loads > 500,000 copies/ml in GEMINI & recent studies is generally small. These small numbers are also seen in other contemporary studies. For example, in the GS-1489/1490, the proportion of participants with baseline viral load >500,000 c/mL has not been reported. However, the number of participants with baseline viral load >400,000 in the GS-1489/1490 & GEMINI studies are comparable: 18 participants on dolutegravir/lamivudine in GEMINI studies [Orkin et al CROI 2021] versus 20 participants on BIC/TAF/FTC in GS-1489/1490 [clinicaltrial.gov]. With no difference in response rates seen in both arms. Additional data to support the efficacy of DTG/3TC in patients with baseline viral load >500,000 c/mL are available from the STAT study and real-world evidence. In STAT, 19/131 participants had baseline viral load >500,000 c/mL, 10 of whom had viral load >1,000,000 c/mL. Of the 17 participants who remained on study (2 participants withdrew), 13/17 (76%) had HIV-1 RNA 500,000 c/mL initiated treatment with DTG/3TC (12 of whom had >1,000,000 c/mL); 16/18 achieved viral suppression at Week 24 (Dou EACS 2021). Finally, the Dovato SmPC does not restrict the use of or urge caution in people living with HIV with VL > 500,000 copies/ml: 'Dovato is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.' We request this caveat to be removed. 2. It is not suitable for those with a CD4 count	Thank you, we acknowledge your points regarding CD4 and viral load. The option to remove these restrictions was put to the whole writing group and the decision was near unanimous to keep these restrictions based on: 1) GEMINI baseline viral load restriction 2) Outcome difference by baseline CD4 at weeks 48 and 96 – week 144 endpoints are not included as a critical endpoint as not all registrational trials report out to 3 years STAT was a single-arm study so not high quality and the numbers with very high viral load are small

			"While treatment failures in those with a CD4 count Longer term data from GEMINI (Week 144 data) show no significant difference in virologic suppression between those with baseline CD4 count ≤200 or >200 cells/mm3 (Orkin et al. CROI 2021) . Additional data on the effectiveness of dolutegravir/lamivudine in patients with low CD4 count are available from real-world evidence. In one real-world study, 45/51 patients with CD4 count < 200 cells/mm3 All 27 were suppressed by Week 12. Multivariate logistic regression analysis indicated that none of age, opportunistic infections, CD4 cell counts 100,000 copies/mL were statistically significant determinants of viral suppression at week 12 (Deng et al. BMC Inf Dise 2022). In addition, the Dovato SmPC does not restrict the use of or urge caution in people living with HIV with CD4 counts We request this caveat to be removed. 3. It is not suitable for those with HIV-related cognitive impairment In the introduction to section 8.1.1 HIV-associated cognitive impairment, the Writing Group acknowledge that the 'risk factors for the development of cognitive disorders are poorly understood and are likely to be multifactorial.' The Writing Group further state 'Although it is possible that the choice of combination ART that subjects receive may influence cognitive function, this is a controversial area without definitive evidence'. In section 8.1.4 Simplification strategies, the Writing Group recommend 'avoiding dual therapy regimens in individuals with HIV-associated cognitive disorders (Grade (1C).' The rationale behind this recommendation is based upon 'Concerns have been raised regarding the cerebral effects of both PI monotherapy [38] and dual therapies [39]. Such concerns are based on the hypothesis that novel strategies comprise only one or two effective ARV agents that may not adequately suppress ongoing HIV replication in sanctuary sites such as the CNS [28]. The Writing Group then cite a retrospective cohort study of aviraemic individuals at high risk or with symptoms of cognitive impairment where '…no differences in CSF escape or cognitive function were identified between individuals receiving a range of dual therapy regimens compared to those receiving standard triple therapy [46]. However, INSTI containing regimens were predominantly used in the small and heterogenous dual therapy group.' The Writing Group also acknowledge within this section (8.1.4) the limited data available on efficacy and safety of modern dual regimens in the CNS. And conclude that subjects in the studies may have experienced more neuropsychiatric adverse events, though no cognitive adverse events were	Thank you for this comment. At the time of writing, there are insufficient data to recommend the use of dual therapy in persons with HIV with HIV-associated cognitive impairment and this cannot be recommended

			identified in first 48 weeks. Furthermore, in section 8.1.3.3, the Writing Group state that these neuropsychiatric events occur in INSTI based regimens and ' At present, there are insufficient data to support avoiding INSTI-based regimens in individuals with symptomatic cognitive disorders, particularly given the high efficacy and low pill burden of many modern regimens, however vigilance is advised.' In summary, the Writing Group acknowledge that the risk factors for cognitive impairment are poorly understood and multifactorial. The choice of ARV regimen and role it plays in cognitive impairment is controversial without definitive evidence. The rationale behind the recommendation to avoid use of dolutegravir/lamivudine is partly based on potential concerns around suppressing ongoing HIV replication in sanctuary sites such as the CNS. However, these concerns are based on PI monotherapy/older PI based dual therapy. Whilst data on the use of dolutegravir/lamivudine in patients with HIV-related cognitive impairment are not available; the DOLAM neuro sub study assessed viral suppression; changes in neuronal injury and inflammatory markers in the CSF on people switching from a 3DR to dolutegravir/lamivudine. At 48 weeks, HIV-1 RNA remained undetectable in both blood plasma and CSF. There was no evidence of neuronal damage or changes in inflammatory markers in CSF. Unbound CSF DTG concentrations were only 23% of total CSF concentrations, however unbound DTG CSF exceeded the EC50 (0.2 ng/mL) by 8-fold unbound (Tiraboschi etal. CROI 2020). The other concern raised by the Writing Group is on INSTI related neuropsychiatric adverse events. However, the Writing Group acknowledge the insufficient evidence to support avoiding this class of ARVs in individuals with symptomatic cognitive disorders. We request the removal of this caveat. 4. It is not suitable for those diagnosed during pregnancy Data on dolutegravir/lamivudine in pregnancy are currently very limited; however, the language 'not suitable' is suggestive of evidence against its usage. It is also not consistent with the DOVATO SmPC (Section 4.6), which states only 'the safety and efficacy of a dual regimen has not been studied in pregnancy' and 'if a woman plans pregnancy, the benefits and the risks of continuing treatment with Dovato should be discussed with the patient'8 We request change of wording to reflect what is in the DOVATO SmPC Section 5.6 What to start in the context of rapid ART initiation This section discusses the two single-arm studies examining rapid initiation of ART i.e., DIAMOND and STAT. The Writing Group provide an overview of study and	We refer to the BHIVA pregnancy guidelines elsewhere, therefore we have removed this point We have clarified that we mean 'rapid' in the context of no available baseline resistance testing. As ViiV has not objected to our requirement that

			results at 24 weeks 'At week 24, 78% of all participants and 92% of the 111 with available data achieved a viral load less than 50 copies/mL.' The Writing Group also state 'Currently there are no published data on the use of bictegravir/tenofovir-AF/emtricitabine in this setting but based on the head-to-head comparisons with dolutegravir-based ART outlined above, this regimen is also recommended for rapid ART.' We ask the Writing group to provide clarification as to why DTG/3TC is not included as an option for use in the context of rapid ART initiation, despite the availability of data for use in this setting. 5.12 Two-drug injectable regimens: switching in virological suppression We comment below on individual points regarding the recommendation criteria on who long-acting cabotegravir/rilpivrine can be used for. 'Have a significant need for injectable ART' '5.12.1 Service capacity While building capacity it is reasonable for services to focus on the following groups for access to long-acting cabotegravir/rilpivirine: Those most in need: o People who are known to or who express major psychological barriers to daily pill taking o People unable to take oral medication o People who describe a concerning adherence pattern but remain virally suppressed o People who describe a real risk of stopping ART if they continue oral therapy; The recommendation in the draft guidelines is to offer this medicine to those with 'significant need/most in need', with the additional clarification who those 'in most need' provided in Section 5.12.1. By limiting the guidance to this group, The Writing Group recommendations could potentially exclude some people living with HIV who would benefit from a long-acting ARV treatment option. Vocabria injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA By restricting use to those with 'significant need/ most in need', the draft guidelines risk going against the spirit of the recommendation made in Section 3, advocating the active involvement of people living with HIV in decision making:	the use of DTG/3TC first line requires a baseline resistance test, we assume ViiV would support our rapid ART recommendation now the definition has been clarified Thank you – we have rephrased in line with these comments

			'We recommend that people living with HIV are given the opportunity to contribute actively to decisions about their treatment (GPP).' For example, a person living with HIV who meets all the recommended criteria described in the guidance, exercises the opportunity to take an active part in their treatment decision making and requests to go onto cabotegravir/rilpivirine but is unable to demonstrate/articulate a significant need. There is a risk that someone such as this who would benefit from a long-acting ARV treatment regimen would be denied access. We request the Writing Group to remove the word 'significant' and change the wording to 'Have a need for injectable ART' or alternatively recommended to 'people living with HIV who face challenges taking daily oral ARV therapy.' Furthermore, the recommendation refers to those with 'major psychological barriers to daily pill taking' but doesn't elaborate on what those may be. Some of the psychological barriers to daily pill taking include fear of disclosure, and/or stigma as well as a daily reminder of HIV status. Risk of disclosure and unwanted reminder of HIV status are called out as examples of intrapersonal barriers to ART uptake/ adherence in Section 6.1.2 (Barriers to adherence) of the draft guidelines. These issues affecting people living with HIV are outlined in the NICE Final Appraisal Document which acknowledge that 'Cabotegravir with Rilpivirine meets an unmet need for people living with HIV-1 by offering an alternative to daily oral regimens.' The NICE Committee also concluded that Cabotegravir and Rilpivirine may be '…valued by people concerned about stigma and disclosure of their HIV status, and it reduces the burden of taking daily tablets' and 'Cabotegravir with Rilpivirine would be beneficial for people who find daily tablets challenging or who would prefer an injectable regimen.' We request the Writing Group to remove the word 'major' and provide clarification/examples of what some of the psychological barriers to daily oral taking may be. 'Have been virally suppressed to Regulatory agencies (the MHRA and the EMA) authorised the use of Vocabria and Rekambys for adults who are virologically suppressed (HIV-1 RNA We request the Writing Group change the wording to reflect the clinical indication in Section 4.1 of the Vocabria and Rekambys SMPCs.	These have been outlined at length in other sections Thank you – the writing group believes a 6-month period of suppression remains a valid recommendation considering the lack of real-world data and that the average duration of suppression at entry to ATLAS-2M was significantly longer. BHIVA is not obliged to follow SmPC advice and there are other examples in these guidelines where we have not done so

			'Accept the risk of virological failure despite complete adherence (approximately 1 in 70 at year 1 and 1 in 60 at year 2).' (And Section 5.12.1 Service Capacity 'acceptance of small risk of virologic failure with resistance.'). The rates of virological failure (VF) as described in the draft guidelines give the impression that there is a cumulative risk of failure as each year passes. It is important to note that the majority of confirmed virologic failures in the ATLAS-2M study occurred in Year 1 (at Week 48, 9/12) with 1 additional participant meeting the CVF criterion between Week 48 and Week 96 and 2 other participants meeting the CVF criterion after Week 96 (Overton et al. CROI 2022) In addition, the draft guidance doesn't provide necessary context to the risk of virological failure which can be reduced by taking into account the three baseline risk factors identified in the Week 48 multivariable analysis (MVA) of the Phase 3 studies [ATLAS (Q4W) FLAIR (Q4W) and ATLAS-2M (Q4W & Q8W)] (Cuttrel et al. AIDS 2021). A combination of at least two of the following baseline factors may be associated with an increased risk of virological failure: archived Rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m2. We request the Writing Group clarify the risk of virological failure is not cumulative and provide context on how baseline factors from the MVA can reduce risk of CVF. 'And have a body mass index of The phrasing of the statement above may lead to confusion with the expectation that people living with HIV who wish to receive cabotegravir/rilpivirine LA injection must have a body mass index of We therefore request that the highlighted wording in Section 5.12 and 5.12.1 is changed to be consistent with Section 4.4 of the Vocabria and Rekambys SmPCs; 'before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m2. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m2 or HIV-1 A6/A1 subtype.' 5.12.1 Service Capacity: 'It is worth noting that the estimated staff resource used to model costs in the National Institute for Health and Care Excellence (NICE) Technology Appraisal was	There *is* a cumulative risk of virological failure with each year that passes. There were more virological failures at year 2 than year 1 and at year 3 than year 2. The quoted figures make it clear that most failures were in the 1st year. We have added some text about baseline factors but there is insufficient evidence at present to draw firm conclusions from the multivariable analysis Thank you. Our recommendation is that where no baseline resistance test is available, we recommend people have a BMI <30 and are not subtype A1/6 which is essentially the same as the advice you have outlined, so this remains unchanged. BHIVA can make more conservative recommendations than the SmPCs Thank you for the comments – although CARISEL shows the time included in the NICE appraisal was an under-estimate. We have not further amended

			15 minutes of Band 5 nurse time.' 'Implementation work shows they can expect to spend 30–60 minutes in clinic at each visit.' We would like to clarify that the 15 minutes of Band 5 nurse time quoted in the NICE HTA appraisal referred to the time it would take to administer the two IM Injections. Evidence from the CARISEL EU Implementation Study showed that administration time reduced with repeated visits. For example, at Month 4, 51% (n=206) of patients reported spending less than 40min in clinic (which included waiting time, injections, as well as time for completing questionnaires) and 84% (n=216) of study participants reported waiting 20-minutes or less (58% reported < 10 min) in the examination room to their injections (Holcqueloux et al. EACS 2021). We request this evidence is included in the BHIVA Guidance to give both people living with HIV and healthcare professionals a clearer idea of how the appointment visit time may change over time as they gain experience so that they can plan accordingly.	the guidelines but have made it clear we will update as new evidence emerges. Service models vary significantly so we look forward to evidence describing real-life experience from UK clinics to better inform the next guidelines update
			We recommend a careful approach to the initial use of long-acting Cabotegravir/Rilpivirine, recognising: • The variable capacity of services to deliver 2-monthly injections at a time when many are still relatively constrained secondary to the impact of COVID-19.	Thank you- amended accordingly
			We note that recommendations regarding the implementation of cabotegravir/rilpivirine are made to take into account the impact of COVID-19 on clinical services. However, considering the lifespan of the BHIVA Guidance (approximately 5 years), we request the Writing Group provide clarity or signpost their expectations once the impact of COVID-19 has reduced and feasibility of implementing of a long-acting treatment in the future. In addition, ViiV Healthcare is committed to working with the NHS to support the implementation of the long-acting cabotegravir/rilpivirine.	
			6.2.3.3 Switching from Efavirenz, Etravirine or Nevirapine to long acting Cabotegravir and Rilpivirine 'We recommend 4-weekly Intramuscular Cabotegravir/Rilpivirine in the first instance when switching from efavirenz- or etravirine-based therapy. Consideration can be given to 2-monthly injections after the first 3 months AND 'An oral lead-in period of 4 weeks is recommended for patients switching from efavirenz/etravirine (GPP), comprising: oral Cabotegravir and higher-dose oral Rilpivirine (50 mg) for 2 weeks followed by 2 weeks of standard dosing or standard-dose oral Cabotegravir and Rilpivirine with additional two-NRTI cover	Thank you - we have removed the recommendation for monthly dosing. However, until more real-world evidence emerges, the writing group has decided to keep the advice about OLI. This can be amended if indicted in the future. After careful discussion the committee has voted to deliver advice that is more conservative than the SmPCs and would like to highlight that cabotegravir and dolutegravir are

			from tenofovir-DF (or tenofovir-AF) plus emtricitabine or lamivudine.' As stated in the draft guidelines, four-weekly IM Cabotegravir and Rilpivirine is not available in the UK. Furthermore, the available formulation, Cabotegravir (600mg/3mL) and Rilpivirine (900mg/3ml) has only been studied (and is therefore licensed) for two initiation injections (one month apart) followed by two-monthly continuation injections thereafter only (regardless of the oral ART regimen switched from) as detailed in Section 4.2 of the Vocabria and Rekambys SMPCs. These licensed recommendations were based on the clinical studies which included patients who switched from NNRTI-agents (see below). Therefore, the recommendations in Section 6.2.3.3 of the BHIVA Guidance are outside of the product licence and not aligned to the data from the Cabotegravir and Rilpivirine Clinical development program. The recommendation for an oral lead-in with an alternative 50mg Rilpivirine dose or the addition of NRTIs after a switch from Efavirenz is not in line with the Rilpivirine or Cabotegravir tablets' SMPCs. Switching without dose modifications is also allowed in the Dolutegravir/Rilpivirine SMPC. Of note, in Section 6.2.3.1 of the draft BHIVA Guidelines, it states that 'it has been shown that switching from Efavirenz to Etravirine or Rilpivirine, or Nevirapine to Rilpivirine in people living with HIV with an undetectable viral load does not compromise virological responses, as undetectable viral loads were maintained despite the transitional lower drug plasma concentrations post-switch.' Considerable clinical trial data exist to inform this switching situation . Data from the ATLAS (Q4W) and ATLAS-2M (Q4W and Q8W) studies show that the majority of participants who switched from NNRTI-containing regimens (most commonly Efavirenz 32% and 39% in ATLAS and ATLAS-2M respectively) where the dose of oral Rilpivirine was not increased, showed that virological suppression was maintained during the oral lead-in and subsequently on LA cabotegravir/rilpivirine well after the residual induction affect from Etravirine/Efavirenz had worn off. There were no CVFs during the oral lead-in phase in those switching from Etravirine or Efavirenz during the period of concern from residual induction, without additional ARTs being required. In the ATLAS trial (Q4W), 155 study participants started cabotegravir/rilpivirine by standard oral lead-in, followed by the four-weekly LA injectable regimen. In the ATLAS-2M trial, following standard oral lead-in, 151 (four-weekly) and 156 (eight-weekly) study participants, respectively, began injectable therapy. Week 48 snapshot analysis outcomes for these participants were similar to the subgroups switching from other 3rd class agents (PI or INSTI) (Swindells et al. NEJM 2020; Overton et al. Lancet 2020). Additionally, pooled pharmacokinetic analyses from SWORD-1 and SWORD-2 with	different drugs, so SmPCs for dolutegravir-based products will not be considered here

			the two-drug regimen Dolutegravir/Rilpivirine showed that Rilpivirine trough concentrations were comparable to historical controls at weeks four, twenty-four and forty-eight following switch from an INI-, NNRTI-, or PI-based regimen using the standard 25mg dose. Additionally, Dolutegravir and Rilpivirine trough concentrations were measured over time during the initial post-switch period in the first 20 subjects (in the NNRTI subset who switched from Efavirenz or Nevirapine to Dolutegravir/Rilpivirine). These extra sampling results showed that the Dolutegravir and Rilpivirine pre-dose plasma concentration (C0) increased from Week two through Week four post-switch (Adkison et al. IWCPAT 2017). Therefore, whilst we recognise the theoretical risk described in switching from NNRTIs to oral Rilpivirine as described in Section 6.2.3.3 of the draft BHIVA Guidance, increasing the Rilpivirine dose during the oral lead-in phase, adding additional NRTI cover and/or administering three IM Cabotegravir and Rilpivirine doses prior to commencing two-monthly dosing is both outside of the licenced recommendations and not supported by the available evidence. We therefore ask Writing Group that the recommendations in Section 6.2.3.3 of the draft guidance made consistent with both the evidence described above as well as the recommendations in the respective Vocabria and Rekambys SMPCs. References: 1. Orkin C, et al. Durable Efficacy of DTG+3TC in Gemini-1&2: Year 3 Subgroup analysis. Abstract 414 2. Study to Evaluate the Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in Human Immunodeficiency Virus-1 (HIV-1) Infected, Antiretroviral Treatment-Naive Adults; Study to Evaluate the Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in Human Immunodeficiency Virus (HIV-1) Infected, Antiretroviral Treatment-Naive Adults [https://clinicaltrials.gov/ct2/show/results/NCT02607930, https://clinicaltrials.gov/ct2/show/results/ NCT02607956] 3. Rolle C-P, et al. Dolutegravir/lamivudine as a first-line regimen in a test-and-treat setting for newly diagnosed people living with HIVAIDS 2021;35:1957–65 4. Rolle C-P, et al. High Rates of Virologic Suppression with DTG/3TC in Newly Diagnosed Adults with HIV-1 Infection and Baseline Viral Load >500,000 c/mL: 48-Week Subgroup Analysis of the STAT Study IDWeek 2021. Oral 75 5. Dou Y, et al. The efficacy of DTG+3TC in naive HIV patients: the real-world data from Southern China. EACS 2021. Poster PE2/19. 6. Deng L, et al. Dolutegravir plus lamivudine versus efavirenz plus tenofovir	

			disoproxil fumarate and lamivudine in antiretroviral-naive adults with HIV-1 infection. BMC Infect Dis 22, 17 (2022). https://doi.org/10.1186/s12879-021-06991-y) 7. Tiraboschi JM, et al. HIV Suppression and changes in CSF Markers in patients randomly switched to DTG + 3TC. CROI 2020. Abstract435. 8. DOVATO 50mg/300mg film-coated tablets GB SMPC. Available at medicines.org.uk – Accessed May 2022. 9. Vocabria 600mg prolonged-release suspension for injection GB SMPC. Available at medicines.org.uk – Accessed May 2022. 10. Rekambys 900 mg prolonged-release suspension for injection GB SMPC. Available at medicines.org.uk – Accessed May 2022. 11. NICE Technology appraisal guidance {TA757}. Available at: Overview | Cabotegravir with rilpivirine for treating HIV-1 | Guidance | NICE. Last accessed May 2022. 12. Overton et al. Long Acting Cabotegravir and Rilpivirine every 2 months: ATLAS Week 152 results. CROI 2022. Poster H03. 13. Exploring predictors of risk factors of HIV-1 virologic failure to long-acting therapy. 48 week MVA analysis of ATLAS, FLAIR and ALTAS-2M, AIDS. 2021 Jul 15;35(9):1333-1342. 14. Hocqueloux L, et al. Perspectives on the acceptability, appropriateness, feasibility, barriers and facilitators from patients receiving Cabotegravir + Rilpivirine Long-acting injectable treatment (CAB+RPV LA): Interim Results from the Cabotegravir And Rilpivirine Implementation Study in European Locations (CARISEL). EACS 2021. Poster PE2/37. 15. Edurant 25mg film-coated tablets GB SMPC. Available at medicines.org.uk – Accessed May 2022. 16. Vocabria 30mg film-coated tablets GB SMPC. Available at medicines.org.uk – Accessed May 2022. 17. Juluca 50mg/25mg film-coated tablets GB SMPC. Available at medicines.org.uk – Accessed May 2022. 18. Swindells S, et al. Long-Acting Cabotegravir and Rilpivirine for Maintenance of HIV-1 Suppression. N Engl J Med 2020;382:1112–23. 19. Overton ET, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. supplementary appendix Lancet 2020; published online Dec 9. http://dx.doi.org/10.1016/ S0140-6736(20)32666-0 20. Adkison et al. Pharmacokinetics of Dolutegravir and Rilpivirine After Switching to the Two-Drug Regimen from an Efavirenz- or Nevirapine-Based Antiretroviral	

			Regimen: SWORD-1 & -2 Pooled PK Analysis. 18th International Workshop on. Clinical Pharmacology of Antiviral Therapy June 14-17, 2017. Chicago, Ill.C.	
	Akbar Jaya	Centre of Excellence for Research in AIDS, Kuala Lumpur	I believe this Guideline of 2022 is much more details compared to 2018 or any previous guideline. All the research present is better in terms of data, especially all those methodological data. The GRADE system is exactly what clinicians needs, to ease during practice. I think this guideline is well-developed.	Thank you
	Simon Collins	HIV i-Base	Thank you to the guideline panel for such a comprehensive update and for all the work that has gone into producing the document. Thanks also for using first-person language throughout. The evidence base for first-line and alternative ART is really clear and helpful and the final recommendations, if followed, will ensure optimal access to the best treatments. It is also appreciated that references throughout the document have been often been updated to refer to modern ART, rather than just relying on historical refs. Thank you for considering the following comments, largely minor. Many of the general comments are based on common reports and from the thousands of questions sent to the i-Base Q&A service each year. However, a couple of sections did not read as equally balancing options (rapid ART, PHI) and some could recognise large changes over the last five years (implications for setting of adherence). Unfortunately, due to limited time, I was not able to comment of Section 8 which rightly brings an important focus to these populations. p1 - Title - Thank you for using person first language. Introduction p6 para 1 - Perhaps point (ii) or (iii) or a new point could refer to management of side effects/tolerability.	Thank you Thank you Thank you Thank you Thank you - added

			p6 para 1 - Please include that people living with HIV will also want to read the guidelines. Later on the guidelines include that readership includes people living with HIV who are interested in this level of detail on their treatment as a third group. This is even though the language is technical. For example, advocates will also use the guidelines for their own care when not strictly being advocates :)	Thank you - added
			Methods	
			p6 - para 3 - The search date cut-offs look as if they should be updated, given the numerous studies that are included but that were either published or presented later.	This was an error, thank you for flagging - it has been updated
			p7 - 1.2.3 - para 2 This para recognises that people living with HIV will be reading the guidelines (see comment above).	Earlier section amended as above
			p9 - 1.3 - para 1 In practice primary aim is to suppress VL to <50 as this is the most accurate surrogate marker for durable clinical benefit. Emphasising this would tighten up the objective of durable viral suppression in all targets for reducing and managing HIV. Leaving it out allows the chance for suboptimal management of detectable VL.	Thank you - amended
			p9 - 1.3 - para 2 The ref for this life expectancy statement is based on results when CD4 >200 (not 350). It is actually slightly less for those with CD4 >350 compared to those with 200-349).	Thank you - we have reviewed the paper in question and the life expectancy statement does indeed refer to people with a CD4 greater than 350. We wonder if you are referring to a UK CHIC analysis published in 2011. We have left this statement unchanged but if we have misunderstood can update in the next version
			However, this paper excluded people with more complex histories, for example, people who injected drugs and those who became positive at birth or early life. So the life expectancy results are for people without these histories and the guidelines should maybe note this.	Thank you, this is an important clarification and has been added
			p10 - para 2 The refs for zero risk of transmission should be clinical studies (for example, PARTNER in JAMA 2016 and Lancet 2019. Community websites could be included as a reference when talking about the social response, but clinical guidelines for	Thank you - amended accordingly

			something this important should also include the studies that produced the evidence. p10 - para 6 (last para) It might be more appropriate to refer to the price of ARVs rather than their cost. The price charged is also open to change based on supplier policies. The overall costs of providing ART are driven by the prices charged by drug manufacturer's and suppliers, and drive prescribing guidelines, even though other costs are involved. p11 - para 2 Suggest that 'regional' can now be dropped from: "We support regional and national prescribing algorithms..." as the NHS has now moved to national prescribing to support equal access. p11 - para 2 - last sentence. "that reducing treatment costs should not be at the cost of an increased risk of poorer treatment outcomes and quality of care..." Perhaps reverse this statement to be more direct and positive - ie that optimal clinical care is the drive for prescribing, and that this will always overcome drug pricing when this is clinically needed etc. Section 3 p.13 - thanks for including this section that emphasises option for people living with HIV to be actively involved in their care. Also for the recommendation to audit these outcomes as active referral to peer support is likely to be very variable in different clinics and populations. p.14 - para 4 Small point but the sentence "Disclosure of HIV status to the GP..." should specify that this is self disclosure, not disclosure by the HIV clinic. p.14 - para 5 - thanks for referencing the nice meta analysis reporting that peer support is associated with better clinical outcomes. I hadn't seen this before. Section 4	Thank you - amended where appropriate Simplified to just ‘prescribing algorithms’ Thank you - amended accordingly Thank you Thank you - clarified

			Rationale p15 - para 3 Perhaps delete 'immediate' or replace with suggested time. Use of 'immediate' could be more precise or specify early on that the same word is often used to cover same day, same week and within two weeks etc in different settings. And to refer to the later section in guidelines with the discussion of rapid ART.	Thank you for flagging this - we have left 'immediate' in place but clarified what this means for the context of these guidelines
			p15 - para 4 The discussion on absolute risk is difficult without saying that delayed/deferred ART was to CD4 350 - which is the UK definition for late diagnoses. These two issues can't be consistent: late diagnosis can;t also be discussed as optimum time for ART based on low absolute risk. Otherwise all the emphasis on earlier diagnosis in national policies is undermined by saying that is doesn't matter much in absolute terms from being diagnosed late.	Thank you- we have amended the text in line with your comments
			Same-day ART initiation p15 - final para " including the lack of proven benefit for same-day ART in a UK or similar setting..." Please could this section this include language that recognises equipoise - presumably there is also no evidence showing a benefit of delaying access to ART in a U setting (compared to same-day ART.	'or harm' added for equipoise
			BHIVA guidelines used to refer to rapid ART as being within about a week, and that this included same-day ART for people where this is possible within the structure of clinical services. Rapid/same-week ART will still be covering the clinical decisions about starting ART without results from drug-resistance and other tests (HBV, HLA etc). p16 - first para, second bullet. " and this is clinically appropriate." Consider deleting or rewording. Current wording makes it sounds like rapid ART is clinically appropriate, whereas	We have now stated 2–4 weeks as this is the usual interval for receiving all baseline results

			the meaning is probably to not be an option that would be clinical contraindicated - for example with some complications in advanced infection when OIs would be treated before ART. p16 - final bullet list Perhaps add new bullet to recognise a commonly reported benefit: "• Reduced stress for people while they wait for more test results. Rapid ART actively does the one thing that reduces HIV risk and lets someone and return quickly to a normalised social situation thanks to U=U." p17 - para 1 " Of note, a French cohort study demonstrated worse retention in care at 1 year among people who started treatment earlier" This is not an appropriate reference for the context of rapid ART. It is observational data where earlier diagnosis and earlier ART were also confounded by having more advanced seroconversion symptoms and more advanced HIV in the early treatment group - both of which are well-established as risks for faster progression and increased mortality. This study primarily shows changes of care over many years when standards of care also changed - linked for example to progressive policies to have more frequent HIV testing - and that were similar in the UK. p17 - para 2 "A qualitative study in Rwanda..." Given that lack of UK data are used as a caution against rapid ART above, it is strange to reference social studies against rapid ART from studies in very different social settings as a reason to delay ART. The two approaches are not consistent. 4.5 Impact on transmission p23 - recommendation bullet 3 Maybe reduced transmission during breastfeeding to be discussed those where	Thank you - amended to: 'and has no clinical contraindications' Thank you - we already discuss more rapid suppression so have amended the second bullet to reflect this point We already acknowledge confounding - specific caveats regarding advanced/symptomatic HIV added. As one of the very few cohorts investigating impact of timing of ART initiation on retention in case, we have kept it in – we make it clear that it was not specifically about same-day ART As the only published qualitative study at the time of writing, we think it is important to include. Caveat regarding applicability to UK added Amended to: 'where relevant'

			this is likely relevant (based on age, sex etc) - rather than with all people with HIV. p23 - audit outcomes bullet 2 As above, maybe the denominator for breastfeeding and maybe vertical transmission should not be all people living with HIV. p24 - rationale line 5 - refs - Quinn et al (NEJM 2000) should really be referenced as the original cohort study that showed the relationship between viral load and transmission risk and even without ART there were no transmissions below about 1500 c/mL. The text could be modified so this can be included. This isn't academic, it shows that data supporting U=U have been around almost as long as ART and that it isn't just a recent event. p24 line 10, last sentence As well as noting HPTN052 and PinP were largely heterosexual, could this sentence add 'and condoms were also commonly used'. p24 line 12 'context of suppressive ART' - please add '(viral load <200 copies/mL)'. p24 line 15 Perhaps say: "after more than 100,000 times that gay and straight couples had sex without condoms" p24 line 16 As above: (i) viral suppressions should be defined as <200 copies/mL. (ii) the reference for clinical results should be clinical studies, not the U=U campaign, which can be referenced for other reasons. p24 lines 20-22 Now these 2022 guidelines only recommend INSTI-based first-line ART this para would be more appropriate to lead with the more rapid viral suppression that will also support earlier U=U. Longer time to suppression should be referenced for people not using BHIVA 2022 recommended first-line ART. Important to be up to date on this. p24 lines 22-24 (last sentence)	As above Thank you - reference added Thank you - added Thank you - added Thank you - amended Added Agree, amended accordingly We do not only recommend INSTIs, the options in certain situations are still recommended. We have amended this paragraph to focus on INSTIs

			Please could the panel consider revising this last sentence which is too impractical and vague. Rather than positively supporting U-U it seems to be undermining people confidence by needing recent VL and living under the treat of viral failure. Firstly, the reference to only relying on recent viral load results makes it sound like people should be responsible for having additional tests. Even before COVID, VL once a year was okay for people on stable long-term ART, and more people might be doing this post-COVID. If the panel want people to have a viral load test every six months, then it is important to say this here. Secondly, the context for U=U is that the risk of viral rebound with good adherence is very low. It might be netter to say this, emphasising adherence. Plus, even if viral load is detectable at low levels is unlikely to change the risk of transmission - just our data is only for <200. UK-CHIC I think reported <5% a year once someone has been stable for the first two years, p25 line 2 - if it hasn't been globally defined earlier, please define 'durably suppressed. *Section 4.6 not using ART* p25 3rd bullet recommendation. HIV services do not have the authority to contact sexual partners of people living with HIV to disclose HIV status. Certainly not because someone has not yet started ART. ART is a medical treatment for the benefit of the person taking treatment. U=U is only a very useful secondary outcome. Sexual health services should be contacting sexual partners about PrEP. These discussions with people attending sexual health services can't be linked to knowledge the clinics have that their partner is HHIV positive. p25 Rationale The rationale paragraphs are very wordy and a bit worrying. There are lots of reasons why someone with high CD4 count and low viral load might decide to wait a little. This choice is supported by evidence, including from START, which wasn't able to show clinical benefits in those with VL <3000 c/mL. These people are not elite controllers but maybe slow progressors (or just in early infection with good set-points. This info need to be included before rushing to psychological assessments. It is	Amended. The frequency of VL monitoring is within the remit of the monitoring guidelines Thank you - amended to remove the unintended ambiguity

			also not appropriate to bring transmission risk into this discussion again, especially linked to psychological assessments. Please pull back a little, condoms are still available and work if people are sexually active with partners who are not living with HIV. Even if the panel are thinking of people who decline ART at much lower CD4 counts, this should be specified. P29 *Stopping ART* first bullet - please add or modify to cover research - ie 'except as part of a clinical study.... etc" p29 *Rationale* Please could these bullets include 'being a participant in a clinical trial that involves interrupting ART.' *Section 5: what to start?* The recommendations on choice of ART and the data supporting them are good, including for INSTI-based ART as first line. p31 line 3 - the reference to the monitoring guidelines could perhaps comment that these are from 2019 if COVID has reduced the need for frequency of some tests. p31 line 4 - pls specify whether or not this should include integrase, Table 5.1 • Columns could have headings. • Maybe drug column could follow the same order throughout: ie always putting the NRTI component last. Then the three DTG regimens can be grouped together to make the pattern easier to see at a glance. • The notes about EFV could be more direct - ie: "Only to be considered during TB treatment and possibly pregnancy, and then switched afterwards". Sections 5.2 to 5.5 summarising evidence for each drug and major combinations is a really helpful review. I am sorry that I haven't had time to review to details to comment but I am sure everything will be accurate. *Section 5.7* P44 - *Rationale*	Thank you. We have deleted a sentence in the rationale about psychological intervention (that is encompassed in the preceding sentence) The availability of condoms is implied in the bullet point about HIV prevention. We have added a sentence about allowing time if necessary for people at low short-term risk Added Added Thank you The reference states the year, and these guidelines are currently under review This may change so specific details avoided deliberately Thank you - added and re-ordered accordingly It is clear that the recommendation is during pregnancy or TB treatment only

			As this section emphasises the primary goal of becoming undetectable with high viral load (usually linked to recent infection), it might be good to explain that time to becoming undetectable can take significantly longer for some people than the 1-3 month goal when starting with lower viral load. This will prepare people to be less anxious if viral load persists at relatively low levels for many months, possibly more than a year, especially given the pressure to be undetectable. A study at CROI a few years ago reported that a larger reservoir in early infection was linked to the longer time to viral suppression, and that modifying treatment is not needed. This will also stop doctors suspecting adherence problems which will help patient/doctor relationship. (Halvas EK et al. CROI 2019, Oral abs 23. Reported here: https://i-base.info/htb/35801). The study was later published (Clin Invest . 2020 Nov 2;130(11):5847-5857. doi: 10.1172/JCI138099. 5.9 *Switching* P45 Recommendations First bullet – thank you for recommending that people already on stable first-line ART with combinations that are no longer preferred, should have the option to switch to match the new guidelines. This is really important. Even with the BHIVA recommendation to review ART annually, this often doesn't happen. We hear of many cases where ART is sometimes not reviewed for many years, sometimes for more than a decade. Even in the context of good CD4 and VL results, older combinations can be linked to poorer quality of life from low-level side effects that are not seen with more modern ART. Many people living with HIV might not be aware that the guidelines have been updated or they might not otherwise be offered newer options. Changing treatment can be stressful – even when the new combination is very likely to be much better. Most people do not realise that as long as viral load is undetectable at the switch, they can return to the older combination if for any reason there are problems with the new meds. If the guidelines can include this somewhere, people are likely to switch earlier. Perhaps add a bullet: • If people are worried about switching, it can be helpful to let them know that so long as viral load is undetectable at the switch, they can return to the older combination if needed.	Thank you - reference added and text amended Thank you - recommendation added accordingly

			5.10, Table 2 P47 – Given the earlier evidence review, it is strange to see ATV/b included as a PI without an example of when this might be used.	
			5.12 – CAB/RPV-LA P56 - *Recommendations* Perhaps add a note that this section of the guidelines is based on limited research and so might be updated before the next guideline update. Some of the bullet recommendations are to limit the risk of viral rebound with perfect adherence. However, these cases might be explained by other factors, or some of the listed factors might not prove to be so important with more research. P 56 - Bullet 7 Perhaps add a new bullet that makes it clear that accepting the risk of viral failure despite perfect adherence will have implications for HIV transmission if someone currently relies on U=U. The two new cases presented at CROI 2022 of viral rebound detected at the routine two monthly monitoring reported viral load levels of roughly 24,000 and 59,000 copies/mL when transmission could easily occur. P 58, final bullet While prioritising some groups makes sense, presentations at the 2022 BHIVA conference included many people who were blocked from changing to CAB/RPV-LA because they didn't meet these criteria, even though demand was actually very low. If there isn't a huge demand for this option it is a shame to make the barrier to access too high for the people who actually want to try this new option. P 59 Recommended criteria As with comment for p56, the bullet on accepting the risk of viral failure should also explain the implications this will have for U=U. Section 6 - *Adherence* P62 – Rationale First sentence: "high levels of adherence" In case this isn't covered later, it would be helpful to set adherence expectations in 2022 with modern treatments. The 95% goal that is historically quoted was from 1998 (Patterson et al.) when ART was less effective and pill counts were much higher. Several recent reviews have reported that even dropping to 80% could be enough to maintain undetectable viral load. The background could	There are several options in this table not recommended earlier. The table includes rationale for where ATV/b may be necessary The section is based on evidence from large, randomised, registrational trials and it is unlikely that high-quality evidence to the contrary will emerge soon; a line has been added to the methodology section about timing of updates Added The first bullet point has been amended to lower the barrier Added Thank you for this elegant comment. However, we believe it goes beyond the remit of the guidelines.

			comment on different definitions of this target: is this a percentage of individual ARVs (one FDC counts as three doses), or of pills? Some studies reported selective adherence, only missing the proble0matic meds rather than the whole combination. So this will mean different things for FDC vs separate drugs. Even though the ideal target is 100% (however defined) it helps people to know about the likely few hours window either side of a dose time when being a little early of later is fine with the PK of modern ART. Perhaps discuss whether there is greater flexibility once reaching <50 c/mL compared to just starting. This could reference the various reduced ART studies (to 5 or 4 doses a week) and include the concerns of increased inflammatory biomarkers and related clinical events that were highlighted in invited lectures at BHIVA 2022. P67 – please could you include pill box in the bullet list of suggestions. P74 – 6.2.1.1 The info about the Liverpool Drug Interaction website could mention that HCV and COVID interaction databases are included, that the site is available in Spanish and English, and that other factsheets cover gender affirming hormones for trans health. Section 7 – *viral failure* P80 – 86 Please could the guidelines clearly state that any suspected viral rebound should be confirmed with a second viral load test on or close to the day that detectable viral load results are reported. i-Base get a calls where some clinics tell the person to return in 3-6 months for their next routine VL. Cases of true viral failure will likely have rebounded to much higher levels and risk of more extensive drug resistance. The current section doesn't discuss natural variability of test results at low levels when there is no statistical different between undetectable <50 (maybe at 49) and any result <100. It also doesn't mention test error. P91 – bullet 6 – perhaps also include 'named patient'. Section 8 – *Specific populations* **Section 8.1** HIV-associated cognitive impairment is a complex and multifactorial issue, with limited data. Although lots of the references are very old, it is good that this section has been expanded to cover more recent research.	We state that high levels of adherence are needed for modern combinations too and, for this version at least, do not plan to include less frequent intake studies or PK forgiveness, especially in the absence of pharmacodynamic data Thank you - we have added the point about gender-affirming hormones but not included HCV and COVID for these guidelines as the relevant drug–drug interactions are also included on the HIV site and the other sites signposted from the HIV site. As national guidelines, we have not added the Spanish language option Thank you - amended This is addressed in section 7.2 Thank you - this is more the remit of the monitoring guidelines and we will forward this comment to that writing group Added: 'We recommend consideration of clinical trials or expanded access programmes to facilitate the previous recommendation (GPP)'

			8.1.2 when to start Rationale - final sentence. As with other comments throughout the guidelines, this sentence is historical and no longer makes sense in the context of the universal recommendation to start ART after diagnosis. **8.1.3 - what to start** bullet 1 - perhaps specify DTG- or BIC- as current guidelines. But is there a need to cover the mood changes reported in a small percentage of people using DTG, and therefore also likely with BIC. bullet 2 -More direct to say not to use EFV (than EFV-containing etc) refs Ref 34 - abstracts shouldn't be referenced unless < 3 years old. Ref 56 - should link to results rather than the trial listing,	Thank you - please note this is now section 8.6 based on re-ordering Thank you for this comment. This recommendation has now been reworded Neuropsychiatric side effects are covered in the mental health section and we do not want to duplicate here Reference 34 is not published. Given that this is an important study, it is still included in the reference list
			4.4 Treatment of PHI p19 - general comment: Currently the rapid-ART and PHI-ART sections to not sit well together and are not approached consistently with the same approach and treatment. The rationale for earlier ART during PHI lists many potential advantages that would be equally appropriate to earlier/rapid ART in the section above, where these reasons have not been included. In the context of ART being recommended at any stage and any CD4 count the emphasise on PHI is not clearly resolved without explaining that symptoms in seroconversion. This section is based on historical context when not treating in PHI lead to deferred ART often for many years - until CD4 dropped to <500, <350 or even <200. This is no longer the case, when missing PHI rolls over to immediate	Apologies, we have endeavoured to align them better There is clear evidence supporting immunological/reservoir benefits for immediate ART for PHI, there is not for same-day ART in the context of non-acute HIV. Taking control and rapid viral suppression are now included in the same-day ART section We accept that the context has shifted but evidence for PHI treatment means deferring ART for a month or two could result in relative harm; we cannot say the same for people newly diagnosed with established infection. We therefore added the

			ART.	following: 'While immediate ART is recommended for all people with HIV, PHI is a unique situation in which starting ART as soon as possible may confer benefit over deferring ART for even a short period of time, such as within 2 weeks. This should therefore influence advice when counselling someone with newly diagnosed PHI, which should reflect that the risk of harm if deferring ART is likely to be greater than for established infection. HIV services should ensure that there are pathways for rapid assessment of people with PHI'
			p19 - last para It is confusing to list low CD4/high VL in the same sentence as short test intervals because these parameters are all related. By definition, diagnosis in earlier Fiebig stages will have the lowest CD4 and VL, so CD4 and viral load need to be looked at within Fiebig stages.	These are all related, so high VL AND low CD4 count are observed in very acute infection. Feibig staging is a research tool based on antibody evolution; this is not a routinely available test and so should not be used to direct recommendations for our guidelines
			So people in stages V and VI and still within 6 months will be after VL and CD4 set points, and after seroconversion symptoms. At the moment, the text is making recommendations using 6 month window based on data from using a 3 month window.	The definition of PHI in the field tends to be within 6 months of a previous test. There is a varied definition of viral set point and again it is no longer relevant for treatment guidelines - this is all research
			The potential benefits of reducing viral reservoir are linked to even earlier ART, when each weeks earlier might have potential clinical benefits - but not when the window is extended to six months.	See references above - agree that the evidence suggests that the earlier ART is initiated the lower the HIV reservoir by current measures. The clinical implications of this remain uncertain though and are not the only reason to start ART
			[The two main differences for PHI are: (i) worse prognosis with low CD4 and high VL - which would also cover people considering ART at any stage. and (ii) preservation of immune function with reduced reservoir. Increased testing, especially in gay men, means that perhaps 40% are diagnosed in PHI and this could also be referenced.]	This is true but also there are specific issues around this scenario in PHI where the data demonstrate that these individuals tend to have been diagnosed in acute infection and have a better prognosis for immediate ART in this setting For all people living with HIV who are diagnosed with low CD4 and high VL, expedited ART is recommended but in the context of PHI evidence

				suggests that much improved long-term prognostic markers result from expedited ART while the same is not available for later-stage disease
			p20 - para 1 This reference is to starting ART within 3 months of early diagnosis, not 6 months.	Many of the references look at different parameters from 3 to 6 months after PHI; this is not to say it is not relevant for those diagnosed between 3 and 6 months. A 2013 paper shows this quite neatly - for each month deferred after acute infection, benefit is less but not significant compared with chronic infection https://pubmed.ncbi.nlm.nih.gov/23323898/
			p20 line 6 - Unless there are differences in recommended ART (unlikely, but pls reference if based on recent data, then there is no reason to include this sentence: " Certain ART combinations may be better tolerated in association with symptoms of PHI" Or maybe say there is no difference between any of the first line ART.	Thank you, we have amended this to: 'Consider choice of ART regimen in the context of same-day ART initiation and side effects that overlap with PHI symptoms'
			p20 Last sentence above Table 4.1: "however baseline viral sequencing is recommended" Please specify if this includes sequencing integrase. I don't think this is done by the previous sentence makes this unclear.	Currently baseline integrase sequencing is not recommended in the UK. This is the remit of the BHIVA monitoring guidelines
			p20 - Table 4.1 These reasons should mainly be similar to the example for rapid ART. They should be used for both examples. Currently the two sections are not consistent and the examples seem to have been picked to support the writing panels personal preferences.	There is no proven immunological or reservoir benefit of starting ART on the day of diagnosis versus weeks/months later in the context of established infection
			Some of these reasons seem historical - ie when ART was delayed until CD4 counts dropped and doctors needed to show clinical reasons to justify earlier prescribing. In the context of universal ART at any CD4 count, I wondered why the guidelines still make a general issue about PHI - everyone will be starting ART anyway.	The paragraph added to rationale (as above) explains why we believe PHI warrants specific recommendations
			p21, bullet list. Some of the points are also not strictly true. For example, CD4 depletion during acute ART (ie in the gut) occurs during the first three weeks and is not reversable.	Thank you. We do not think we have robust enough data using current ART to say that there is no impact on GALT reservoir and immune recovery

			This shouldn't be included in a general argument for starting within the first six months. If still leaving this in, perhaps reference Brenchley/Douek (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2211962) - maybe with this more recent paper too (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6701936/) p21 - 3rd para "there is never likely..." - There never will be - fact :) This whole paragraph is redundant though in the context of universal ART. The small percentage of people who wait a while before starting ART are also likely to wait if diagnosed in PHI (I think). p22 - lines 1-3 - although these sentences sound convincing, they are only really accurate with specific periods. There isn't a linear relationship between the reservoir and time to ART. The main window to reduce the reservoir is in early Fiebig stages well before most people are diagnosed (including those in SPARTAC). There is maybe another breakpoint - a few months later where the difference in much smaller. After this, there isn't a smaller reservoir when starting after two years vs three years etc.	after 3 weeks from AHI. We will consider adding the references suggested to the next guidelines update Thank you - we retain some optimism so have left this sentence unchanged. For the reasons outlined above we do not think this is redundant Thank you. Given that we do not have the perfect viral reservoir assay that predicts clinical outcomes we have left this section unchanged at present. The current evidence from laboratory assays is that the sooner ART is started from diagnosis of PHI the lower the reservoir is, which then remains reasonably stable while on suppressed ART and continues to reduce slowly for 7 years on ART. The characteristics of the HIV reservoir in PHI are different from later stages of disease by most current assays (TILDA, IPDA Q4-PCR) as it is more homogeneous and potentially more susceptible to further interventions, but this is all unknown for clinical outcomes at this stage. We have not added more detail to these guidelines but will consider doing so for the next update
			Section 4.7 controllers The section title could be changed, perhaps to: 4.7 Managing slow progressors, viral controllers and elite controllers p26 Comment - this section seems confused about the different terms and doesn't even refer to LTSPs. It might be good to start with the consensus definitions (though these are not always consistent. line 1: "4.7.1 Definition of viral controllers (also known as elite controllers) "	In our commitment to person-first language, we have kept the section title unchanged Thank you. We believe that all these definitions are out of date with the current evidence for ART recommendations. We know that CD4 counts above 500 still do not necessarily reflect normal immune function and data from START and TEMPRANO

			This is not correct. EC specifically maintain VL >50 c/mL without ART, sometimes specified for a minimum number of years. Plus keeping a CD4 >500. Viral controllers allow viral load to be generally controlled and stable over time, for example 50 - 2000 c/mL. Long Term Slow Progressors (LTSPs) (previously called non-progressors) - is just based on immune response - ie CD4 staying above 500 - and any level of VL. LTNP was changed to LTSP because over time most of the people in this group do slowly progress. line 2 : " Viral controllers are defined as: " This should be 'Elite controllers" (because it specifies VL <50)	demonstrated survival benefit so these terms are no longer relevant for guidelines. The only clinical question in terms of the role of ART is for those rare individuals who were referred to as 'elite' controllers, who have sustained (>1 year) HIV VL <50 off ART with normal CD4 counts and CD4:8 ratio of >1. We have not made any changes to this version and have emphasised that we are referring to people with undetectable HIV-RNA off ART and normal immune parameters
			p26 Recommendations Bullet 1 only covers half the issue. It says ECs with progression should start ART. It also need to talk about ECs with stable lab results that are not showing progression. There are of course all sorts of potential benefits of ART, but no evidence to show any clinical benefits.	We have added the following: 'We recommend that ART is discussed with all people, but for those with spontaneous viral control and normal immune markers off ART, there is a lack of high-quality, long-term, clinical outcome data on or off ART. Other benefits of ART include confidence in durable viral suppression (and zero risk of sexual transmission) and reassurance that ART will prevent disease progression'
			The guidelines could perhaps reference the potential for natural eradication given enough time and the examples of Loreen Willenberg and the Esperanza patient etc). The guidelines should recognise that ART was not used in the first case saving 30 years treatment an related impact on quality of life.	We have not included these rare cases as they do not impact recommendations
			Bullet 2 doesn't make sense. Anyone not on ART should of course continue to have VL and CD4 monitored. More direct wording would also help explain the next five indented criteria. p27 Recommendations	While we accept this may be stating the obvious, we disagree that it does not make sense. The point is to dispel any myths that 'elite controllers' do not need as regular monitoring as anyone else not on ART. The bullet points relate to situations where remining off ART is not recommended and, on review, we think this is clear
			3rd bullet - sounds good but how are ECs going to be monitored for malignancies?	In the same was as anyone living with HIV: symptoms, weight, routine blood and urine markers, and specific screening in line with BHIVA

			p27 - Rationale line 1 - the 1-5% quoted sounds more like percentage of LTSPs. The estimate for ECs (which I this the authors mean) is usually quotes as <1%. The two refs given here don't support 1-5%. ref 1 - Grabar et al. 0.4% LTNP, 0.15% EC ref 2 - Sajadi et al. 1.1% incidence of EC There are likely dozens, likely hundreds of papers reporting percentages in different cohorts, most at <1% Although some cohorts report higher figures, averaging these out will keep at closer to <1%. For example a recent paper from the Congo report ECs at about 5% (Berg et al) https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00051-7/fulltext line 5 really needs correcting. It wasn't "a few participants" with VL <3000, it was 1 in 4 - closer to about 1150 as 3000 c/mL was the cut-off for the first quartile. This might change how the panel interpret the START results, as a sub analysis of people with VL <3000 didn't show clinical benefits from earlier ART. last sentence - good that the uncertainly of management of this group (whatever group the panel are focussed on) - being more specific is important and the term 'long term viral controllers' is confusing. 4.7.2 - should this be elite controllers rather than viral controllers? p27 - Without know the viral load cut-off being referred to the last paragraph on p27 does not make sense. p28 4.7.3 - *Summary* line 2 "withheld" doesn't sound right - this is more likely to be the person deciding that they don't want to use ART - so no-one is withholding it.	monitoring guidelines (e.g. cervical screening) and national screening (e.g. general population bowel cancer screening). We have added some detail to the summary accordingly: 'Monitoring for comorbidities should be in line with BHIVA monitoring guidelines, national screening guidelines (e.g. population bowel cancer screening) or as indicated based on symptoms and/or laboratory abnormalities. We do not recommend enhanced screening in people with spontaneous viral control off ART' Thank you - corrected to 'several' As above Thank you - 'withheld' has been changed to 'a decision to defer ART is made'
			8.3 CVD	

			8.3.1 - The reports of integrase inhibitors increasing CVD risk could perhaps be acknowledged in the text, given the time before the next BHIVA update. The guidelines could comment on potential options if the data continue to support a link. This includes Neesgaard et al and the accompanying editorial comment that highlights a concern for all current first-line ART. https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(22)00094-7/fulltext	Thank you - we have added a sentence summarising this trial, the RESPOND reference and a cohort from the US showing lower risk of CVD on INSTI
			8.3.3 weight gain p119 - Please could the panel review the final sentence which currently recommends people continuing ART that is contributing to excessive weight gain. There may not be any evidence to support switching ART, but the guidelines need to cover management of weight gain in women on current first-line ART, expecially black women, given the results from ADVANCE. This could affect a significant percentage of women The guidelines cannot recommend combinations that are all associated with weight gain in African women and not to support changing ART, which would be recommended for any other serious side effect. The weight gain in ADVANCE doesn't reach a plateau but so far continues for years with extended follow-up. As guidelines now recommend monitoring weight on ART, they also need to cover excessive weight gain that is othewise unexplained.	Thank you - we have added some detail around switching and general support. As more evidence emerges we will add detail
			8.4 Women 8.4.2.2 - please include side effects reported in the ADVANCE study which was powered to show the sifnificant differences in women. NOTE: If not already included, this should be included as a caution in Section 5: What to start. 8.4.2.5 - Menopause Given the increasing focus on menopause at BHIVA conferences and that UK has leading experts, it woud help to expand this section to highlight issues linke to care in the following selected studies. Dragovic B et al. Menopause care in women living with HIV in the UK - A review. J Virus Erad. 2022 Mar; 8(1): 100064. doi: 10.1016/j.jve.2022.100064	Thank you - included in section on women. Please note this is now section 8.10 based on re-ordering Thank you - more detail will be included in the next update

			Solomon D et al. The association between severe menopausal symptoms and engagement with HIV care and treatment in women living with HIV. AIDS Care. 2021;33:101–108. Tariq S et al. PRIME (Positive Transitions through the Menopause) Study: a protocol for a mixed-methods study investigating the impact of the menopause on the health and well-being of women living with HIV in England. BMJ Open. 2018;9 doi: 10.1136/bmjopen-2018-025497. King ME et al. Menopausal hormone therapy for women living with HIV. Lancet HIV, 2021. DOI:10.1016/S2352-3018(21)00148-X 8.4.4 - physchological issues. Please include body shape changes and weight gain. **8.5 - Mental health** bullet 2 is important enought to be clearly included in Section 5 on what to start. This can't just be in Section 8. Perhaps reword the bullet given the last sentences in this section. It would be clearer if the bullet starts by saying clearly that INSTI are still recommended ast first-line in people with mental health history, but that this should include additional careful monitoring. **8.8 Older life** 8.8.2 - first bullet Unclear why these criteria are still needed given guidelines recommend ART for everyone after diagnosis. **8.9 Transgender** 2nd bullet - perhaps specify clinic use the two-step question for collecting data on gender.	We will provide more detail on weight for the next update Thank you for this comment. We do not include specific recommendations for specific populations in section 5, hence the separate section 8 for specific populations Thank you for this comment. We feel it is important to include this recommendation to ensure all people, including older persons with HIV, have access to recommended ART regimens Updated
	Ben Cromarty	UK Community Advisory Board	**4. When to start** Section 4.3 (Individuals presenting with AIDS or a major infection) discusses populations that should start ART immediately. But Section 8.1 (specific populations – HIV-associated cognitive impairment) also recommends immediate ART…is this covered by 4.3, or suitably signposted?	Section 4.3 recommends that all people with an AIDS diagnosis should start ART immediately, with the exception of TB and cryptococcal meningitis. 'HIV encephalopathy' is an AIDS diagnosis; we believe that section 8 and section 4.3 are congruent on the point that people with cognitive impairment likely to be due to HIV should start ART immediately

			There is no discussion about how the person's readiness to start ART should be assessed...indeed, it is barely mentioned. EACS have a table that illustrates how to assess a person with HIV's readiness to start. Something similar should perhaps be include in the BHIVA guideline. While the recommendations may be OK, I think the rationale is less than ideal. I am not sure about the use of the term 'immediate", as in "All consensus HIV treatment guidelines recommend immediate ART initaton, regardless of CD4 count"…I would prefer to see a clear statement along the lines of: "People with HIV can start ART as soon as they are ready. For most people, this will be soon after they first test positive. However, each individual is different and their needs and readiness to start ART should be discussed and assessed in the initial meeting with the members. Although it is possible to start on the same day as diagnosis, this is not generally a medical necessity (though there are special circumstances such as low nadir CD4 count, pregnancy or other where immediate starting is necessary – discussed in section XX). Bear in mind that a new diagnosis can be a shock for the individual, and they may need time and support to come to terms with this. ART should only be started if the individual is ready, unless there is a strong case for starting immediately." This is more important than going into reasons about why same-day ART initiation may or may not be relevant... **6. Supporting people on treatment** It is good to see that there is a section on supporting people on treatment. There is useful input on adherence and drug interactions. But there seems to be a key omission...one of the most important times when support is needed is on and immediately after diagnosis, and when discussing ART and when to start. In order for the clinical team to make an informed assessment, together with the person living with HIV, several things need to be in place. There needs to be some understanding of the issues by the person with HIV, which may need information to be given in an accessible way. And there needs to be a thorough assessment of the patient's needs...clinical, psychological and other...so that an informed choice can be made. Maybe it's a given for clinicians to do this automatically....but EACS spell out the kind of things that should be considered at an initial assessment...this seems helpful. Peer support will also be helpful at this early	One of the recommendations in section 3 is: 'We recommend following the European AIDS Clinical Society (EACS) guidance on assessing readiness to start and maintain ART (GPP)' Thank you. We have addressed these points by incorporating the EACS guidance on assessing readiness as a recommendation in section 3, and by altering the text in section 4.6 Thank you - we have added some text to section 6.1 in line with these comments

			stage. Whether this discussion goes in here (Section 6) or in when to start (section 4) is another question…	
			7. Managing virological failure There is no discussion on how to support patients at this time, neither here in this section, nor in section 6. Yet this can be an extremely concerning time for patients, and support may be needed, to help establish the causes of virological failure (often poor adherence) in a way that does to apportion blame or stigma to the patient. And the patient may have genuine concerns about what "failure" means, especially if there is resistance and a change in regimen is needed...and more so if treatment options are (increasingly) limited. All this seems to me to require a lot of information and support to be given to the patient...yet no mention is made of this, nor of what support might be needed. Again, this discussion could go here in this section (7), or in section 6.	Thank you - we have added a comment and referred to section 6
			8. Special populations This gives a lot of useful information in how to deal with specific populations, who may require changes to when to start, and what to start with. It might be helpful to have some mention of this in section 4 (and maybe 5), highlighting that these sections are for the "general" cases, but that there are many times where special considerations are needed as described in section 8. So ideally, the healthcare team should first assess the patient needs, to be sure that they do not fall into any of these special populations, before deciding when and what to start with. But I don't think this is mentioned in either section 4 or 5. Again, maybe it's a given that clinicians do this sort of assessment...but it perhaps should be mentioned...signposting details in section 8...along the lines of : "Before deciding when to start ART, and with what regimen, it it critical to assess whether the patient falls into any of the special population categories: then list these...OIs, TB, comorbidities, pregnancy, kidney disease, CVD, mental health…etc..." and signpost section 8 for more detailed discussion.	This would all be part of a standard assessment and, in the final guidelines, a summary of the recommendations will come first so all recommendations can be viewed together
			8.1 cognitive impairment How is HIV-associated cognitive disorder determined? Some signposting at least to how this is done may be helpful. Depression and anxiety should be considered and ruled out, presumably? EACS have an algorithm for diagnosis (and management) of cognitive impairment which could be used?	This is covered in the BHIVA monitoring guidelines and the BHIVA psychological standards document

			8.4 Women The guideline highlights that there is insufficient data to support specific recommendations for non-pregnant women with HIV, so the general recommendations for ART are used. But it also says that women may experience more AEs ,or more intense AEs, than men, and this may lead to issues with adherence and discontinuation, particularly in some some populations. Perhaps there should be more support offered to these groups, in terms of raising awareness and offering peer support?	We agree and the importance of peer support is referenced through the BHIVA monitoring and pregnancy guidelines
			8.5 Mental Health What screening is done to see whether or not there may be concerns for issues around mental health for someone starting ART or on ART? Should this be signposted?	This is part of the monitoring guidelines
			There is no discussion of the potential interaction between drugs used for treatment of mental health issues and ART. Although this is covered in general terms in the section on drug interactions, should mention be made of this?	We think the general advice to check for drug–drug interactions is sufficient
			8.10 Chronic Liver Disease This section doesn't seem to have the same format - no recommendations?	Thank you - amended. More detail will be provided in the next update
			Signposting to how liver disease is assessed? (Eg EACS?)	
			Other Comments Should there be something about ART in IDUs?	Good point - we will pass this on to next committee for consideration
			Should there be a general introduction to the section, highlighting that many conditions that might at first seem like "special populations" (such as those with diabetes; COPD; undergoing cancer treatment) have not been included because (other than considering DDIs) the treatments for these are essentially the same as for anyone else?	Thank you- added
			Should there be signposting to co-infections with TB; HCV covered in separate guidelines?	Thank you - added

Comments from UK-CAB community consultation 11/08/2022				
	UK-CAB member		**Submitted in advance:** concern re lack of detail on weight change on ART and management	Detail beyond scope at present but more detail will be considered for next iteration Information on general advice, support to switch and relative advantages/disadvantages added
	UK-CAB member		**Submitted in advance:** what support can 3rd sector share or support for people with spontaneous viral control? Some people in this group are resistant to starting ART	Agreement that we do not cover the psychological aspects for people with spontaneous virological control and will put this forward for consideration in the next update We have added a line acknowledging the importance of peer support and consideration of psychological support
	UK-CAB member		**Submitted in advance:** if we consider the baseline factors that predict virological failure on injectable ART, are we over-stating the risk of virological failure? Concern that we include virological failure rates in the recommendation and that this is overly negative	Complicated as some people experience virological failure even with zero risk factors. Line added to acknowledge that there are some factors that may increase the risk of VF but there is a lack of data and guidelines will be updated as evidence emerges Acknowledged - removed from recommendations and added to main text
	UK-CAB member		**What about ageing and HIV?**	There is a section on later life which is deliberately brief at present due to limited evidence We have added 'ageing with HIV' in title so easier to find as per discussion at the community consultation