12 July 2016
EMA/CHMP/EWP/672442/2015
Committee of human Medicinal Products (CHMP)

Overview of comments received on 'Guideline on the clinical development of medicinal products for the treatment of HIV Infection' (EMEA/CPMP/EWP/633/02 Rev. 3)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA - Pär Tellner (par.tellner@efpia.eu)
2	European AIDS Treatment Group - EATG
3	Bristol-Myers Squibb (BMS)
4	Gilead Sciences International Ltd.
5	Paediatric European Network for the Treatment of AIDS (PENTA)

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	EFPIA welcomes the opportunity to comment on the draft revision 3 of this guideline. In general, the information provided in the revised draft guideline is less clear than the information in the previous version of the guideline. The proposed definition of trial populations is based on practices applied in clinical trials which are not considered to be feasible in daily clinical practice (e.g. genotyping might be not be available/performed). The revised draft guideline is expected to provide more guidance on the trial design for simplification or switch therapies. The guideline is also expected to show a more holistic regulatory view on the clinical development, defining what type of data would need to be collected during the clinical trial phase versus the type of data expected to be generated by post-authorization studies in the different trial populations. The impact of the revised draft guideline on the existing ART is also to be carefully considered.	For the revision of the guideline a scientific expert group was consulted and there was a general support among the experts that study populations and treatment indications should be categorised based on the presence or absence of relevant drug resistance, rather than on “treatment experience”.

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	Pricing & reimbursement implications of the revised draft guideline are to be evaluated (e.g. how will changes in the indication wording and in the development plan, supporting the file/indication, impact the outcome of HTA assessments? Is non-inferiority acceptable to HTA bodies?) We also regret that there is no mention of Annex A & B in the revised draft and would appreciate to know if and when these annexes are to be revised and made available. We have identified four areas of concern, which are detailed below, where more details, clarifications and revisions of the proposed requirements would be helpful. 1. A Sponsor may wish to develop and register a new dosing regimen for an already marketed compound (i.e. going from a twice daily dosing [BID] to a once daily [QD] dosing). Similarly, a Sponsor may wish to develop a new formulation of an approved compound to enhance its pharmacokinetics or allow for FDR/FDC development. The guideline does not clearly address considerations for such development programs. The CHMP should make provisions in the guideline for such programs in which a streamlined development program could be envisioned. Alternatively, the CHMP should clarify whether the guideline, as currently written, is sufficiently applicable to such programs. 2. There are products in development that are pursuing less frequent administration (e.g., once weekly, once monthly, once every	The current guideline provides guidance on section 4.1 of the SmPC which is specific for the therapeutic area. For all other section of the SmPC the general SmPC guidance is applicable.

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	3 months). The guideline makes no mention regarding such development programs. Therefore, it is unclear what additional requirements, if any, may be needed should a Sponsor plan to pursue such a development plan. The CHMP should clarify whether the guideline, as currently written, is sufficiently applicable to such programs. 3. There are products in development that may afford the benefit of an improved safety profile relative to the leading agent within a class. Although the guideline goes into extensive detail regarding the different study designs for patients requiring a switch due to virological failure/lack of viral suppression (Section 3.4.3), the guideline makes no mention of a development program that incorporates a switch for tolerability purposes. Therefore, it is unclear what additional requirements, if any, may be needed should a Sponsor plan to pursue such a development program, and, if pursued, the implication for the label (in particular, with respect to the indication) to reflect the results from such tolerability-switch studies. The CHMP should make provisions in the guideline for such programs. 4. The proposed definition of trial populations is based on documented viral resistance rather than treatment histories. As written, this guideline may not align with the upcoming FDA guidelines (Guidance for Industry: Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment, June 2013, Clinical Antimicrobial, Revision 1) where patient populations are still defined based on treatment experience. Different definitions of	Comment noted. Applicants are encouraged to seek scientific advice/guidance for development programmes not included /discussed in detailed in the current guideline. Comment noted – see previous comment.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	patient populations in FDA as compared to EMA guideline might provide a challenge for designing clinical trials in a global development program and for adequate description of such population in pre- and post-approval documentation.	Comment noted.
2	No comments	
3	No comments	
4	No comments	
5	PENTA generally agrees with the proposed text of the guidelines which address specific issues related to the development of ARV in children. However: 1. We found very interesting and important the suggestion that "early dose" studies could be done in children suppressed on ongoing regimens by adding the new agent. This approach was followed for Etravirine and important PK data were generated (Konigs et al AIDS 2012 26: 447-455). Also a new study on Elvitegravir (GS-US 183-0160) is following the same approach. So we do not understand why it is stated that no PK/PD data are generated with such a study design which on the contrary we feel very useful and innovative. 2. 24 or 48 weeks for efficacy in ARV naive or switching for second line in failing patients: we don't think that 24 weeks data are good enough as we know that VL often is not suppressed by 24 weeks especially if we consider a VL < 50 or even lower an endpoint (Penpact 1 Lancet ID 2011, 11: 273-283). Therefore in this case we recommend to have VL data at 48 weeks 3. 24 or 48 weeks for efficacy in already suppressed children (simplification strategy): here we are looking at a risk of possible VL	Comment noted. Longer-term follow-up beyond 24 weeks will be covered in the post-marketing phase as 24 weeks is usually considered as sufficient for recommending marketing authorisation in paediatrics.

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	rebound which usually occurs soon after switching. In this case 24 weeks could be theoretically fine. However data from PENTA18/Koncert (Lyall Late breaker CROI 2014) showed that a significant number of patients rebounded between 24 and 48 weeks. Therefore 48 weeks is recommended. 4. 24 or 48 weeks for toxicity and tolerability: It depends on the toxicity profile of each drug. However, in general, metabolic, renal and bone toxicity can occur later than 24 weeks, so a a minimum of 48 weeks follow up is recommended. 5. 24 or 48 weeks for adherence: 24 weeks could be enough for an initial evaluation of adherence. However is we want to measure the “Forgiveness of non adherence” or the "adherence-resistance relationship” a longer follow up may be needed	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
55-63	1	Comment: Definitions of treatment naïve and treatment experienced have been revised in this draft guidance. Specifically, mentioning that the term “treatment experienced” is not used in the revision for not adequately defining a patient population with drug-resistant viruses. However, in line 627 the term “treatment experienced” is used. We recommend that line 627 is revised according to the statements in lines 55-61.	Comment noted and accepted.
55-63	1	Comment: The proposed term treatment-naïve refers to both treatment history AND viral resistance. One direct consequence and concern is that the proposed terminology may exclude a large group of patients, i.e. treatment experienced patients without viral resistance (e.g. most patients failing a first-line PI based treatment do not show evidence of resistance). If this group of patients is not studied within a clinical trial, it is unclear how this would be addressed in the label. For consistency with the revision of the trial populations based on documented viral resistance, it is proposed to define the term treatment-naïve patients	Comment noted. More clarity is provided in the executive summary.

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		as those 'who are infected with HIV without mutations conferring drug resistance in their major viral populations' versus those 'who are infected with HIV harbouring drug-resistant virus'. In this way, no reference to previous ART use is included, leading to a clearer definition.	
55-63 and 157-158	1	Comment: While it is acknowledged in the guideline that phenotypic assays are hardly used in clinical practice and that the focus should therefore be on generating genotypic data, it is of importance to note that the collection of genotypic data is not widely spread in Europe in daily clinical practice. In current treatment guidelines genotypic testing is recommended (but not mandatory) before initiating ART. This could lead to a divergence between the naive population in clinical studies and the naive population in clinical practice, where info on genotype is not always available. As an example, it is known from recent cohort data (EDURANT/EVIPLERA) that the 'Number of patients with documented pre-treatment screening for ARV RAMS, including resistance screening up to 5 years prior to baseline', is very limited (approx.. 10%). The collection of genotypic data, or even viral load	Comment noted and accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		data, may also be missing in certain countries.	
70	1	Comment: "placebo-controlled superiority designs are no longer feasible and non-inferiority trials in such populations are fraught with methodological problems". This would create challenges for HTA purposes. We propose to include the option to test for statistical superiority, if non-inferiority criteria have been met, by a pre-specified testing procedure.	Comment noted. Applicants are encouraged to refer to other relevant guidelines mentioned in section 1.
73-76 and 239-250 and 373-376	1	Comment: It is not clear how to extrapolate efficacy and safety data from treatment naïve to "treatment experienced". If treatment experienced patients are not studied, this will be problematic in HTA usage. The guideline should state the evidence needed to demonstrate that extrapolation is valid. We recommend that guidance is provided on valid extrapolation.	Comment noted. The indication will be treatment of HIV infection and the medicinal compound to be used will be on the basis of absence of relevant drug resistance.
73-76 and 239-240 and 404	1	Comment: The following is not covered in the revised guideline: development of new agents of existing classes in patients infected with virus with resistance to other classes. Except the 'worst-case' scenarios on extensively drug resistant virus, covered in section 253-258.	Comment noted. The executive summary has been revised.
79 and 430-433	1	Comment: Design of studies "treatment experienced" (studies that include patients with viral resistance (…..)). It is not evident that it is feasible to start	Comment noted. Section has been revised.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		studies when patients receive their failing regimen. If failure is detected, patients will receive an alternative treatment immediately, time horizon might not be sufficient to include patients in the study.	
83-84	1	Comment: There is an ambiguous statement related to agents "….not suitable for study in treatment-naive patients (e.g. injectable agents) would need to be discussed on a case by case basis." The CHMP should make provisions in the guideline for development of such compounds including long-acting formulations and it would be helpful if a specific patient population is recommended for the development of injectable agents.	Comment noted. Applicants are encouraged to seek scientific advice/guidance for development programmes not included /discussed in detailed in the current guideline.
152	1	Comment: It is not clear whether phenotypic investigations are required for the development of all compounds. Current clinical guidelines suggest that genotypes are all that are required and indicated for treatment-naïve patients. The guidance might also be different for the development of FDC of existing compounds.	Comment noted.
184	1	**Comment**: *In vivo* pharmacokinetics: We would suggest the addition of the following text to this section: **Proposed change (if any):** "For studies with long-acting injectable drugs, PK studies with the oral formulations would generally be acceptable to describe clinical pharmacology in special	Comment noted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		populations (renal and hepatic impairment) and for drug interactions if pathways of metabolic and excretion are comparable."	
191-192	1	**Comment**: The guideline states that determination of drug concentrations in CSF and genital secretions should be considered, although the clinical significance of these data is at present unclear. This requires additional consideration. It would be helpful to outline the circumstances when this would be required. Additional guidance regarding methodology for obtaining and reporting drug levels in tissue would also be helpful, including clarification of the desired study population (healthy subjects vs. HIV patients), utility of PK endpoints (AUC vs. single time points), and value of reporting unbound fraction.	Comment noted. The text in the current guideline is considered adequate; however Applicants might consider seeking scientific advice in this regard.
202-207		**Comment**: We would propose that drug interaction studies are only required if *in vitro* data (transporters, enzymes, etc.) suggest a potential interaction. Otherwise, the list of scenarios could be very broad. With respect to the examples mentioned, we would suggest that in view of the aging HIV-infected population, drug-drug interaction studies with anti-diabetic (type II) medication may be considered for inclusion in the interaction study programme. **Proposed change (if any):**	Not accepted. The text in the current guideline is considered appropriate.

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		We would suggest adding the following sentence: "In the initial development programme it is recommended that priority be given to DDI studies with other drugs for the treatment of HIV *that are likely to be co-administered in Phase 2 and 3 studies and for which clinically relevant interactions are possible*." And Include as an additional example of metabolic abnormalities.	
225-229	1	Comment: The guideline refers to current regimens as being generally 3 active drugs, with or without an enhancer. The situation where a 2-drug regimen would be appropriate is not mentioned in the guideline. It is important for the guideline to acknowledge that as new drugs are developed with improved safety, efficacy, and pharmacokinetic profiles, future regimens may not require 3 drugs, provided clinical trial data support such an approach. There are several recently published studies supporting the potential for NRTI-sparing regimens containing 2 anchor drugs (i.e., SECONDLINE, Lancet 2013; EARNEST, IAS 2013), and the results of additional studies are expected in the near future. As currently written, the guideline does not discuss the	Not accepted. The current text in the guideline is considered appropriate and allows covering for other future development scenarios.

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		potential for NRTI-sparing regimens. We would suggest that the guideline mentions this future paradigm-shifting potential. Specifically, addressing additional requirements, if any, needed to support approval for regimens containing only 2 drugs.	
239-243	1	Comment: We would recommend to mention that only 'in absence of known cross-resistance to the new class' randomized, controlled double-blind studies in patients with fully drug susceptible HIV might suffice to support use in all HIV-infected subjects'. Otherwise, clarification is needed on how further information needed in patient populations not studied with the new agent of a new class will need to be generated.	Comment noted.
244-250	1	**Comment**: The reference made to 'use in class-naïve patients' is confusing, as it is not clear if this refers to viral susceptibility or previous treatment history, of which the latter does not seem to be in line with the viral susceptibility at the basis of this revised draft guideline.	Comment noted. In this regard, more clarity has been provided in the executive summary.
277-278	1	Comment: The guideline should specify that a validated assay be used for measuring LLOQ. The assay should also be commercially available.	Comment noted.
279-281	1	**Comment**: The use of the FDA snapshot algorithm will be considered appropriate to assess whether the suppression of the plasma viral load can be maintained below the LLOQ of the HIV-RNA assay used (i.e. preferred primary efficacy criterion). It should be complemented with a secondary TLOVR analysis based on a confirmatory measure of VL.	Comment noted and accepted.

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		Since both analyses provide similar statistical results and the FDA snapshot analysis is easier to apply, what is the added value of the TLOVR algorithm, which requires additional programming, in view of the fact that other sensitivity analyses will already be included alongside FDA snapshot analysis (e.g. missing = failure). In addition and given the difference in stringency between FDA snapshot and TLOVR, borderline results in one assay might provide divergent outcomes in a secondary assay.	
282-284	1	Comment: "... In addition to the proportion of patients reaching the <LLOQ endpoint the proportions with viral loads falling into pre-defined strata (e.g. 20-49, 50-99, 100-199, 200-400 and > 400 copies/mL) should be tabulated..." We consider that three strata are sufficient, i.e. below the LLOQ to 200, 200-400 and above 400. These are more clinically relevant.	The text in the current guideline is considered appropriate and provides examples for stratification.
299-301	1	Comment: We would propose that the guideline stresses that these events are rare and specifically states that AIDS defining conditions are only reported as supportive data. Future studies will likely not be powered enough to draw significant conclusions from differences detected in the frequency of AIDS-defining conditions.	Comment noted and additional text has been added in the guideline more applicable for future developments.

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383-389	1	**Comment**: The guideline indicates that for treatment naïve studies, patients should be stratified by the most important prognostic factors and as a minimum by baseline viral load and CD4 cell count. We would suggest that if the Sponsor feels that another factor would be more appropriate than CD4 cell count, it would be appropriate to substitute with another stratification factor. Knowing that having more than 2 stratification factors may cause analysis problems with too few patients in any one particular cell (stratification by treatment group). Furthermore, Baseline viral load and CD4 are correlated and therefore only one is needed as a prognostic stratification factor. We would suggest deleting “as a minimum” to enable flexibility and amend remaining text to: by baseline viral load or CD4 count” on line 386. While recognising that the ideal trial population will recruit diverse participants (with respect to viral load, optimised background therapy (OBT) activity, viral subtype, sex and ethnicity) the list of desirable characteristics suggested by the guidance requires prioritisation. **Proposed change (if any):** Patients should be stratified for the most important	The text in the current guideline is considered appropriate and provides the examples for stratification based on CD4 cell count as a minimum but not limited to. If the re other important prognostic factors, these should be considered as well.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		prognostic factors and as a minimum by baseline viral load **or** CD4 cell count. *However, CD4 cell count could be substituted in the event another more adequate stratification factors is identified and having more than 2 stratification factors would not be feasible due to expected sparse data issues*.	
395	1	**Comment**: While acknowledging that maintaining the blind is very important, the AE profile of the new drug and of the existing drugs is a given and it might not be possible to "match" the drugs for their AE profile. It Would be better to indicate that measures should be put in place to avoid "inadvertent" unblinding of investigator and sponsor.	Comment accepted.
397-399	1	**Comment**: The guideline states that a study of treatment-naïve individuals should have a primary endpoint of 48 weeks, with a study duration of at least 96 weeks to obtain long-term efficacy and safety data. However, as clearly shown over the last decade, all recently approved agents that were shown to be effective at 24 weeks remained effective at the 48-week timeframe. With this in mind, further rationale should be provided in the guideline as to why a 24-week approval cannot be considered in the treatment-naïve setting, especially for a drug that (1) is a member of a new class, (2) a drug of an existing class with a documented improvement in efficacy and/or safety above existing agents from that class, or (3) a drug with a new treatment regimen (e.g., change from	Comment noted. The text in the guideline has been revised.

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		B.I.D. to QD) or new formulation that has already previously documented consistent efficacy at both the week 24 and week 48 time points.	
416	1	**Comment**: The second prerequisite that such studies be conducted in patients that are in need of the new agent in order to create a likely suppressive regimen implies that it will be highly unlikely that such studies are feasible as the number of patients in such a situation are very small given the efficacy of the current regimens and hence the required sample size would not be reached. It should suffice that they are failing the regimen, even if there are other licenced treatment options still available.	Comment noted.
422	1	**Comment**: Limiting studies to patients taking a drug in the same class at entry will reduce the number of subjects available for an evaluation of safety. Our concern is that limiting the inclusion criteria of the study to subjects with Screening or Baseline class resistance AND taking a within-class drug will limit the capability to do safety evaluations on a broader population (if using a different dose). Therefore, we would recommend limiting the primary efficacy analysis population. **Proposed change (if any):** We suggest editing the sentence to read “Patients to be included in the primary efficacy analysis……”	Comment noted and accepted.
424-429	1	**Comment**: It is considered that baseline and historic	Comment noted.

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		resistance are important information to collect; the resistance status at screening is important for the primary analysis but for the long term safety the option to use historical data is useful as it makes recruitment easier.	
432	1	**Comment**: The design of the functional monotherapy portion of a study in patients with resistant virus is unclear and requires additional explanation. The study design graph and subsequent text suggests that patients are randomised to maintain their failing regimen or to make a within-class substitution to the investigational agent. This comparison cannot be blinded unless placebos are manufactured for every drug in the same class as the investigational agent. We would suggest that the design is amended to randomising subjects to either add the new drug/placebo to the failing regimen or to switch out the failing-same-class drug for the new drug/placebo.	Comment noted. The text in the guideline has been revised.
455-459	1	**Comment**: The staggered design requires that a patient stay on a failing regimen for up to 2 months (~1 month of screening, 2 weeks of placebo, and then 2 weeks of test agent). This approach will likely not be acceptable to providers and patients due to prolonged use of the failing regimen.	Comment noted. The text in the guideline has been revised.
460-466	1	**Comment**: At least 2 doses of the new agent should be considered. In case of inclusion >1 dose (both in functional monotherapy & follow-up study period), how are subjects from the placebo-arm assigned to a	Comment noted.

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		particular dose?	
462-464	1	**Comment**: This is an opportunity for the EMA to encourage sponsors to plan for a robust assessment of activity in patients with in-class resistance. Perhaps this evaluation would be more robust if sponsors could merge their Phase II and Phase III study in this population – thereby reducing the impact of likely slow recruitment on the ultimate time to first filing. Secondly, this setting (slow recruitment, soon-observed endpoint) provides opportunity for adaptive exploration of dose. Perhaps the guidance could encourage sponsors to use this possibility for in-stream adaptation to explore a wide range of doses in an efficient, adaptive setting? **Proposed change (if any)**: A proposal for additional text follows: "... Sponsors are encouraged to explore a wide range of doses in this setting in a Phase II study, using pre-specified criteria to drop doses that yield sub-optimal response. Phase II studies conducted in this way can potentially be expanded seamlessly into Phase III studies, allowing for potential savings in sample size and the continuation of recruitment over a longer period of time. Sponsors considering such designs are encouraged to consult the reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design (CHMP/EWP/2459/02) and to seek scientific advice..."	Comment noted.

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472-476	1	**Comment**: It needs to be specified whether the comparison with Placebo seeks superiority, or else non-inferiority. Or else, 'viral decline' is the difference with Placebo (double delta); but then, what is meant with 'remaining activity of the drug in proportion to that seen in monotherapy studies in patients with wild-type virus'? Is this then also the quantity upon which sample size is based? This section warrants additional clarification.	Comment noted. The text is the guideline has been revised.
483-485	1	**Comment**: It is indicated that an individually optimised background regimen needs to be used in place of a prior failing regimen. It is known that pre-existing mutant viruses may impact the efficacy outcome of a regimen. It would be helpful to include a clear definition on the individually optimised background regimen in this case. If the same class of antiviral agents is selected as OBT for the continuation phase treatment, the chance of virologic failure is higher even if no obvious resistant mutations, based on population sequencing, are detected for the selected OBT because low level of resistant viruses would impact the outcome of long term study. We suggest that the guideline indicates which different class of antiviral agents should be used as optimised background regimen for the continuation phase.	Comment noted. It is difficult to identify upfront which different class of antiviral agents should be used as optimised background regimen as will be determined by resistance tests performed at baseline and the activity of the OBT according to the baseline resistance test is to be evaluated in the continuation phase.
498-507	1	**Comment**: We suggest that the guidance includes a	Comment noted. Applicants are encouraged to consult the

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		clear definition of “a well-documented combination” if the FDC is to be used as replacement.	specific draft guideline on clinical development of fixed dose combinations.
499-510 and 601-603	1	**Comment**: The guideline mentions the need for a safety database of 500-1000 in treatment-naïve patients. However, no recommendation is provided as to the total size of the safety database that would be required for a new drug that is being developed simultaneously as a stand-alone product and as part of a fixed dose regimen (FDR). One could envision that in the future, most new HIV agents would be developed simultaneously as a stand-alone product and a FDR. Such an approach may be possible in the future with ever improving technologies for developing FDRs. Hence, the guideline should speak to the size of the safety database for the stand-alone product relative to the FDR, if the Sponsor was to pursue an approval based on a single Phase 3 efficacy study of the stand-alone product in combination with other anti-retrovirals and a single Phase 3 efficacy study consisting of the FDR (in lieu of a BE study of the FDR). In such a development situation, we would suggest that data for the stand-alone product and FDR be combined to reach a total safety database of 500-1000, in lieu of at least 500-1000 patients for the stand-alone product.	Comment noted, however the text in the guideline in terms of recommendation of the safety database for an initial marketing authorisation is considered appropriate. Applicants are encouraged to seek scientific advice to identify to what extent the applicant might be supported by PK/PD analysis.
546-553	1	**Comment**: The recommendation on studies in	Paediatric clinical studies are expected to lead to the same

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		children is unclear; the suggestion for switch studies in suppressed children is difficult to understand. It should be clarified how a switch study would be justified unless the child is either not suppressed or intolerant.	indication as the one that is anticipated for adults. The guideline does not distinguish between naïve or experienced patients switching therapy but rather focus on the presence or absence of relevant viral resistance(s).
562-571	1	**Comment**: Clarification on the proposed timing of the studies suggested in this section is needed.	The text in the guideline is considered adequate and provides some flexibility on the timing on the generation of data in pregnant women.
621-625		**Comment**: It is important that the virus is susceptible to all ART of the planned regimen, so 'without present or past evidence of viral resistance to agents of the ART regimen' and 'not only of the X class to which the new agent belongs'. We recommend that the guideline covers the following questions: Will 'patients with virus fully susceptible to the drug' automatically include the true 'treatment-naïve' patients (no previous treatment history) as well as the 'patients switching for tolerability reasons' (previous treatment history, but no resistance)? Can ARVs currently having an indication in 'treatment-naïve patients' be considered for use in 'true treatment-naïve patients' as well as in 'switchers' then or will MAHs be required to file for a variation of the indication to change the wording in the indication?	The indication for use of antiretrovirals medicines will be treatment of HIV without any distinction of treatment populations based on the exposure or not to antiretroviral medicinal products. The key factor will be susceptibility to the antiretroviral medicine subject to evaluation.
627	1	Comment: See comment on lines 55-61; The reference to studies in treatment experienced patients, while the definition is not used throughout the rest of the	Comment noted. More clarity in this regard is provided in the executive summary.

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		guideline given focus on susceptibility virus is confusing.	
68	2	Comment: Ritonavir is not the only booster Proposed change (if any): agents in recent years, and to the general use of pharmacoenhancement ("~~ritonavir~~ boosting") when	Comment noted. Accepted.
78-79	2	Comment: "One or more studies" looks vague. Proposed change (if any): the class to which the new agent belongs. In this setting data should be generated from a pre-determined number of~~one or more~~ studies	Not accepted. The text in the current guideline is considered appropriate.
136-137	2	Comment: add CMV to Hep B and C viruses	Comment noted.
181	2	Comment: Proposed change (if any): includes use of a recently developed <u>and approved</u> sequencing method it is recommended that samples should be	Comment noted, however the text proposed in the guideline is considered appropriate.
194-210	2	Comment: substances (such as recreational drugs) and products from plants should be added	Comment noted. The text in the current guideline is considered appropriate.
207-208	2	Comment: interaction with drugs used in the management of substance dependence are considered. Some European countries do use heroin for replacement therapy (like Denmark, Switzerland,), so heroin might be included in the drug-drug interaction studies but not amphetamines or other drugs if "street drugs" are not explicitly mentioned. It is contradictive	Comment noted. General guidance on drug-drug interactions is provided and this is considered sufficient.

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		and particularly with people living with HIV would be important to explore DDI with street drugs. This does not concern only people who have drug dependency and who might be using drugs through injecting but also people using occasionally or episodically. Proposed changes: add recommendations for DDI with street drugs	
212	2	Proposed change: Data derived from the initial studies in healthy subjects ~~may~~ must be used for the preliminary selection of	The text proposed in the guideline is considered adequate.
222	2	Comment: there is no mention here of gender and ethnicity issues (although, further down, it is recommended to include as many women as possible in trials). Renal impairment, for example is more common in black people than in Caucasian people.	Comment noted and accepted.
279-281	2	Comment: The optimal moment to obtain the confirmatory measure of VL is not defined.	Comment noted, information on the endpoint is provided in section 3.4 confirmatory studies.
296-297	2	Comment: CD4/CD8 ratio is now considered as the most valuable inflammatory marker. Why not add it to the list, even though trials considered here are to measure drug efficacy. We can foresee that in a couple of years, inflammatory markers will have to be considered in most efficacy trials.	Not accepted. The current text in the guideline is considered adequate.
303-320	2	Comment: How is Primary infection considered here? Should patients with PI be excluded? Comment: It should be added that during the monotherapy period, all should be done to facilitate patients' access to the trial's site.	Comment noted. Generally marketing authorisation applications are intended for the treatment of chronic HIV infection and the presence of primary HIV infection is an exclusionary criterion.
312-318	2	Comment: It should be added that during the	Comment noted. Clinical trial conduct is outside of the scope

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		monotherapy period, all should be done to facilitate patients' access to the trial's site.	of the guideline.
330-332	2	Comment: specific data for this population to be collected Proposed change: Patients with more pronounced immunosuppression (e.g., CD4+ cells < 200/µL) or symptomatic 331 patients should be included in phase I/II studies only if there is a specific scientific rationale and if 332 promising efficacy and safety data are already available from patients with higher CD4+ T-cell counts. Therefore, specific data from this population (sub-study) should be collected.	Not accepted. The current text in the guideline is considered adequate.
369	2	Comment: Proposed change: required to qualify for a per protocol population. , based on solid background.	Not accepted. The current text in the guideline is considered adequate.
370	2	Comment: "Should aim to enrol…" not strong enough NIH Revitalization Act 1993, Amended October 2001, Inclusion of women & minorities in clinical research. A recommendation to the EMA is to adopt and apply similar conditions to Revitalization act. Proposed change: Confirmatory studies should ~~aim~~ to enrol a representative sample of patients. In particular, sponsors	Not accepted. The current text in the guideline is considered adequate.
556-567	2	Comment: "Older" lack of definition Proposed change (if any): No specific studies are	Comment noted. This section is clearly dedicated to the elderly which worldwide is accepted to be a chronological age of 65 years as per definition of 'elderly' or older person.

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		expected in older patients aged 50 years and older. However, as the lifespan of HIV-infected patients continues to increase it should become increasingly feasible to enrol representative numbers of older	
556-561	2	Comment: The message for studies in older patients must be reinforced. The context is well described but the recommendation does not seem to "match" with it. They only "encourage" recruitment. There have been basically no data on HIV drugs in older than 65 (as seen in many SPCs). And all studies show that PLHIV in developed countries are reaching the same life expectancy as in the general population. Proposed change: no proposal, unless the comment above is taken into account.	Comment noted. The current text in the guideline is considered adequate.
573-576	2	Comment: patients with chronic HCV and cirrhosis are forgotten here. Proposed change: Patients who are co-infected with HIV and HCV and/or HBV constitute an important, and in some sites, large proportion of HIV-infected individuals. Hence, it is important that such patients are represented in adequate numbers in the pivotal studies, to confirm hepatic safety in patients with chronic hepatitis infections, including patients who present cirrhosis.	Comment noted and accepted.
616-619	2	Comment: Patient self-reporting of side effects (as per European regulation) is not mentioned here. The data collected from patients should be included in the long-term safety analyses recommended here.	Comment noted. The safety data provided in a marketing authorisation application derived from clinical studies in which specific safety reporting rules apply. However this is possible and is capture in the product Information for the post-

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			authorisation phase.
623	2	Comment: HIV-2 could be mentioned if relevant. (it is addressed earlier in the development of this document).	Comment noted. The current text in the guideline is considered adequate.
Section 3.1, as of line 224 and Section 3.4 as of line 360	3	**Comment**: for a new agent in a new class, BMS agrees that randomized controlled confirmatory studies in *treatment naïve* patients might suffice to support use in HIV-infected patients, regardless of prior treatment history, and presence of RAMs relevant for agents of other classes. Furthermore, BMS agrees with the approaches for development of new agent in a new class or a new agent in an existing class. **Proposed change (if any)**: BMS proposes that the use of randomized/controlled confirmatory studies in *treatment experienced* patients (with remaining treatment options) demonstrating NI to an appropriate control should be recognized as a design to support use in HIV-infected patients in general. While it is understood that a Marketing Authorisation Application (MAA) should include at least 2 randomized controlled confirmatory studies, BMS proposes that in addition to the approach	Comment noted.

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		proposed in the draft guideline for a new agent in a new class (2 randomized controlled confirmatory studies conducted in *treatment naïve* patients) the guideline reflect that applicants can submit a MAA containing: • 1 randomized/controlled confirmatory study in *treatment naïve* patients, and 1 randomized/controlled confirmatory study in *treatment experienced* patients (with remaining treatment options) to support use in HIV-infected patients, regardless of prior treatment history and presence of RAMs relevant for agents of other classes. Alternatively, if a new agent in a new- or existing class is developed for *non-treatment naive* HIV-patients, BMS proposes the draft guideline reflect that applicants can submit a MAA containing: • 2 randomized/controlled confirmatory studies in *treatment experienced* patients (with remaining treatment options) to support use in *non-treatment naive* HIV-patients regardless of prior treatment history and presence of RAMs relevant for agents of other classes. For a new agent of an existing class BMS agrees that endorsement for use in patients infected with virus that is resistant to some or all of the other	

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		agents that are in the same class as the new agent would require clinical evidence of efficacy as outlined in the draft guideline. The rationale for this proposal is: First, several classes of antiretroviral (ARV) agents provide a variety of treatments with standard combinations that include at least 3 active agents to suppress viremia to undetectable levels, including nucleotide/nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INI), fusion inhibitors, and C-C chemokine receptor-5 inhibitors. Despite the large number of agents, a significant % of patients experience failure of combination therapy within 1 yr of therapy start, due to multiple factors, including viral heterogeneity, resistance, associated toxicity, poor adherence secondary to side effects, and complicated regimens. Transmission of ARV drug-resistant virus in newly diagnosed HIV-1 infection has been documented, with 5-25% of newly diagnosed patients harboring resistance mutations to existing classes of ARV agents.[i,ii,iii] Furthermore, it has been estimated that despite therapy, ~63% of patients on combination	

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		therapy remain viremic with viral loads > 500 c/mL.[iv] First-line combination antiretroviral therapy (cART) options include many highly effective agents having demonstrated long-term efficacy and durability in large patient populations. [v, vi] These typically include a backbone of 2 NRTIs, and the majority of NRTI backbones are available as fixed-dose combinations (FDCs). In addition, several 1st-line regimens for treatment-naïve adults are available as single tablet regimens (STRs), combining all components of a cART regimen into a single formulation. Increased utilization of STRs during 1st-line treatment reflects patient/clinician desire for convenient therapy. However, it also represents a challenge to the selection of subsequent ARV therapy. Specifically, since many STRs have similar NRTI-based components, virologic failure of 1 of the regimens (with emergence of NRTI resistance) may render most of the other available STRs poorly suitable for 2nd-line therapy, or beyond. This can lead to ARV combinations in 2nd- and 3rd-line regimens that may be suboptimal, which in turn may potentiate more resistance. Therefore, a need exists for alternative regimens (mono-entity tablet, FDC in combination with other ARV agents, or STR) with minimal overlap of ARV	

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		components with 1st-line STRs, and that can be used reliably in 2nd- or 3rd lines. To support use of these alternate regimens as 2nd or 3rd line treatments, clinical evaluation in this population (*non-treatment naive*) is appropriate and necessary. Second, in the context of global medicinal development where other Health Authorities require randomized/ controlled confirmatory studies in *treatment experienced* patients to support commercial use in that population. Recognition in the EMA guideline that such a study design could meet the standards of a randomized/controlled confirmatory study may simplify an understanding of the number/design of randomized/controlled confirmatory studies needed to support a global development program that includes the EU.	It should be noted that at the time of the revision of the guideline a scientific expert group was consulted and there was a general support among the experts that study populations and treatment indications should be categorised based on the presence or absence of relevant drug resistance, rather than on "treatment experience".
68	4	In September 2013, cobicistat, a pharmacoenhancement drug was approved in combination with atazanavir or darunavir; Gilead suggests either removing the example in the bracket or adding "cobicistat-boosting" as another example.	Comment noted and accepted. The text has been revised.
122 and 125	4	Consider specifying as "EC_{90} or EC_{95}" as this is dependent on the assay utilized".	Comment noted, however the text in the guideline is considered adequate.
123	4	It is recommended that cell ~~lines~~ types include …	Comment noted and accepted.
150-152	4	Not clear if the guideline is advocating testing all baseline samples regardless of treatment outcome. Gilead suggests that baseline samples from treatment successes should be analyzed as necessary to	Comment noted, however the text in the guideline is considered adequate.

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		determine potential effects of baseline variation on treatment response and this may be accomplished by genotypic investigations or a combination of genotypic and phenotypic investigations depending on the drug target and populations being studied.	
214	4	Consider specifying as "EC_{90} or EC_{95}" as this is dependent on the assay utilized.	Comment noted. The text in the guideline is considered adequate.
279-281	4	FDA validation study and Gilead experience demonstrate that snapshot analyses generate results that are highly consistent with TLOVR analyses; therefore Gilead recommends removing TLOVR as a complimentary analysis.	Comment noted and accepted.
385	4	"stratification" should be "stratified"	Accepted. The text has been revised.
406-409	4	This paragraph should clarify that the clinical studies to evaluate efficacy of a new agent of an existing class should also follow confirmatory studies in treatment naïve patients (Section 3.4.2)	Comment noted.
437-449	4	This section suggests that substitution is a preferred approach to testing a new drug of the same class. However, as also stated, there may be residual activity from the "old" drug which may provide for a mixed antiviral effect during the substitution. Unless there are safety concerns, simple addition of the new agent to the failing regimen may provide the least ambiguous PD response assessment. This section should allow for both approaches, addition or substitution, even within the same drug class.	Comment noted and accepted.
536-540	4	Lines 536 - 540 are endorsed.	Not applicable.

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563-568	4	It is expected that any data would be collected in the post-approval setting. The guideline should clarify this.	Comment noted. The guideline already refers to the need of post-authorisation data.
573-576	4	Assumes that the new ARV is anticipated to be safe in patients with chronic viral hepatitis. This needs to be a consideration for each individual agent under development, including the preclinical and available clinical safety profile; therefore, it is not appropriate to require that Phase 3 registrational trials include HCV and HIV coinfected patients for all new agents.	Comment noted and accepted.
601		Requiring a 48-week safety database could prolong the availability of new agents for patients with high unmet medical needs. Consider 24 week endpoints for populations with limited treatment options.	Comment noted. The guideline already refers that in certain situations, smaller safety database and a shorter expose may be acceptable.

[i] James CW, Moffett LE, Szabo S. Prevalence of antiretroviral drug resistance in antiretroviral-naive individuals. J Int Assoc Physicians AIDS Care (Chic). 2009;8(3):193-5.

[ii] Simen BB, Simons JF, Hullsiek KH, et al. Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. J Infect Dis. 2009;199(5):693-701.

[iii] Little SJ, Smith DM. HIV treatment decisions and transmitted drug resistance. Clin Infect Dis. 2005;41(2):233-5.

[iv] Oette M, Kaiser R, Däumer M, et al. Primary HIV drug resistance and efficacy of first-line antiretroviral therapy guided by resistance testing. J Acquir Immune Defic Syndr. 2006;41(5):573-81.

[v] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Section accessed 17 Dec 2013.

[vi] EACS Treatment Guidelines 2013, see http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf. Accessed 17 Dec 2013.