European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON THE DRAFT REVISION OF THE GUIDELINE ON THE CLINICAL DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF HIV INFECTION - EMEA/CPMP/EWP/633/02 Rev. 2

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Merck Sharp & Dohme (Europe) Inc.	Belgium
2	Schering Plough	Belgium
3	EFPIA	Belgium
4	Roche	Switzerland
5	Sociedad Española De Farmacia Hospitalaria / Spanish Hospital Pharmacy Society (HIV Network Group)	Spain
6	Gilead	United Kingdom
7	European AIDS Treatment Network (NEAT)	United Kingdom
8	European Aids Treatment Group (EATG)	Belgium

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
HIV Network Group: The guideline is very useful to establish the basis for HIV clinical trial methodology. We miss a special consideration about adherence. It is a very important factor related to the efficacy of antiretroviral therapy so clinical trials should indicate clearly how adherence is defined and measured, the causes of non-adherence and the statistical treatment of non-adherent patients.
Gilead: The Company is somewhat surprised how strongly this guidance advocates for short-term monotherapy data in Phase 3 studies, especially in patients with various remaining treatment options at the time of treatment failure (see below).
NEAT: Almost no account on the fact that in non inferiority trials, there should be an advantage to justify the use of a potentially less effective treatment (might be easier to take, better tolerated, ...) that is explored in the trial. No mention on the need to explore severe non-AIDS morbidity such as MI, non-AIDS cancers, renal or liver diseases (the use of HIV-related events including AIDS is not specific enough). It is a comprehensive and excellent document. The only thing I am not quit happy about is "functional monotherapy" in treatment experienced patients with failure. It this really needed when studies can be done in treatment-naive patients with many treatment options in the case resistance to a new drug should develop rapidly (might happen with the most efficient of the new drugs). For naive studies, I think a 1-year, double-blind trial is now too short. These days, almost all naive combinations are effective at week 48. Longer-term safety is what will distinguish regimens. A 2 or 3-year randomized trial with 1-year primary endpoint is not a great compromise, as results get shown while the study is ongoing, which can only corrupt identification and ascertainment of adverse events. Safety and perhaps PK data should also be generated in a geriatric population. Serious non-AIDS events should also be recorded in all phase 3 trials – it may be that regimens have similar antiviral activity and similar effects on progression to AIDS, but have different effects on progression to one or more of CVD, liver failure, fracture, renal failure etc. Switch studies need to be justified, not just performed to increase market share. Therefore, patients should not only be eligible by having RNA <50, but also because they have a definite, drug-related problem for which a switch can be justified, and yet no such a serious problem that the control group becomes unethical. The only reason to switch any patient <50 I can see is simplification e.g. to a pill that is taken less often, has fewer pills per day or is a co-formulation. I think that overall the guidelines are sensible and the diverse nature of the new agents in the pipeline makes it very difficult to be too prescriptive. For example, duration of functional monotherapy in experienced patients should be kept to a minimum and I hope that consultation with EMEA would enable this to be defined for each new ARV. I agree that we should like at HIV 1 subtypes, responses in small minorities, co-infections, children and women. I like the section on patients with limited options and the possibility of using 2 unlicensed medications. I think that drug drug interactions should be carried for all drugs, arv-arv interactions as unexpected interactions do occur. This is particularly important in the setting of advanced patients. I would suggest that drug drug interaction with immunosuppressive drugs be carried out in the post marketing setting as this is very important for those who are transplanted. I wonder whether all licensing studies should include assessment of lipodystrophy, and other metabolic changes not just the NRTI or PIs. Should Ultrasensitive resistance tests be carried out at baseline on those patients who fail during the study in addition to the standard resistance test?

SPECIFIC COMMENTS ON TEXT			
GUIDELINE SECTION TITLE			
Line no.[1] + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**	**Outcome**
EXECUTIVE SUMMARY			
7	Not sure what this means – in relation to what?		Clarified. The design of clinical trials should take generally acknowledged HIV treatment guidelines into account.
10	"Direct–acting anti-retroviral substances" should be defined	Replace the end of the sentence by: *"Anti-retroviral substances, that interfere directly with the viral life cycle, including (and not limited to), surface-binding, fusion, unpacking, reverse transcription, intracellular transport, proviral integration, viral transcription, maturation, assembly, and release from cells. "*	Not agreed. "Direct–acting anti-retroviral substances" is considered to be a clear enough description in the context of the document.
11-13	It should be more clearly defined when Scientific Advice is recommended.		Not agreed. The sponsor is always free to ask for advice. Here it is only stated that this is advisable in case this NfG is not followed and for new classes of compounds. Scientific Advice is also mentioned later in the documents in relation to specific sections (1.2.3 and 4.2.1).
11-13	Paragraph should be written more clearly to better define when Scientific Advice is recommended.		Not agreed (see above).

[1] Where applicable

INTRODUCTION (BACKGROUND)			
22	With newer and more potent medicines the number of agents in a given regiment is yet to be determined. We suggest that a specific number of products be removed from this sentence and the focus be placed on efficacy and minimization of resistance.	*Due to the inherent high mutation rate in HIV,* the combined use of active medicinal products to achieve adequate efficacy and minimize emergence of resistance is considered essential.	Acknowledged, text reworded.
22	It is very likely that HAART does not always means using at least three drugs. Currently there are many trials at using less than three drugs for treatment HIV infection. For example there are going to be trials of dual therapy with boosted PI + integrase inhibitor or boosted PI + CCR5 inhibitor. Another example: in ACTG 5142 the combination of Lopinavir+Efavirenz did as well as triple therapy. It is very likely that, depending on the drugs, less than three might still be optimal therapy.	Delete this sentence: "Due to the inherent high mutation rate in HIV, the combined use of at <u>least three active</u> medicinal products is currently considered essential".	Acknowledged, text reworded.
22-23	In the setting of newly approved active antiretroviral classes, it should be acknowledged that in certain situations it may be reasonable to study 2 drug combinations.		Acknowledged, text reworded.
22-23	In the setting of newly approved active antiretroviral classes, it should be acknowledged that in certain situations it may be reasonable to study 2 drug combinations. The European guidelines from the European AIDS Clinical Society (the	Re-word the sentence lines 22-23 to read: "Due to the inherent high mutation rate in HIV, the combined use of **at** <u>least 2 or preferably</u> 3 active medicinal products is currently considered essential."	Acknowledged, text reworded.

	executive committee includes France, UK, Germany, Ireland, Italy, Switzerland, Belgium, Denmark and Spain) advises that in case of virologic failure with development of resistance it is recommended to change treatment with a suppressive regimen that should consist of 2 or preferably 3 drugs active drugs (including medicinal products from previous used classes).		
23	Clarification required.	ART refers to this combined use of antiretroviral medicinal products	Acknowledged, text reworded.
23	There is nothing magic about 3 drugs. Available data indicate that potent boosted PIs are perfectly adequate as monotherapy. Studies ongoing with PI plus raltegravir also likely to prove highly effective. I think "essential" is too strong. Will be out of date soon, if not already. "Optimal" is probably as far as it should go.		Acknowledged, text reworded.
30-31	It would be preferable to indicate that the information should be accessible to physician and patient rather than that blinding is not expected.	The sentence in lines 30-31 should be rephrased as follows: *"However, results of testing that is utilized in routine clinical management of patients, including CD4+ T cell counts, viral load, and HIV drug-resistance, should be accessible to the treating physician and respective patients."*	Acknowledged, text reworded.
32	As well as geographical differences, should include pts infected with a range of subtypes, if such individuals are available locally		Acknowledged, text added.
34	The sentence starting line 34 should be re-worded to read: *"Therefore for novel compounds with indication of antiviral activity against*		Acknowledged, text reworded to indicate that it is sufficient to show activity.

	HIV that is resistant to many licensed therapies…"		
35-37	This sentence is getting at encouraging sponsors to combine multiple investigational agents but the wording is not clear. Informative and ethically acceptable trials can also be conducted without co-operation between sponsors.	In line 35–36 it is suggested to delete: …"*to co-operate in order to make it possible*"…	Acknowledged, text reworded.
38-40	Clarification is needed as to how the CHMP defines treatment-experienced and what is meant by heavily pre-treated patients. These definitions may vary around the world so unambiguous definitions are needed in this EU guidance.		Clarified. "Treatment experienced" as a general term seems less problematic than the term "heavily pre-treated".
38-40	"Provided that the properties of the experimental agent appear suitable it is expected that safety and efficacy would be evaluated in patients who are treatment naïve and in those who are treatment experienced, including heavily pre-treated patients." This wording tends to imply that studies in either treatment naïve patients only or in treatment-experienced patients only are not supported. It also implies that treatment experienced studies should always include heavily pre-treated patients. Given the number of new drugs approved in the last 3 years, studies in heavily pre-treated patients will be increasingly difficult to show a treatment benefit of the new agent over an optimised background. The guidance should also give		Not agreed. The paragraph emphasis that the experimental compound should "appear suitable" and that "safety and efficacy" should be evaluated.

	consideration to studies to assess the potential benefits of new agents with improved tolerability profiles and new paradigms of combination regimens designed to retain antiviral efficacy but reduce long term burden of adverse events and toleration.		
40-41	The numbers of women, individuals from ethnic minorities and patients co-infected with HBV and/or HCV should be sufficient to allow generalized conclusions on safety and efficacy.It is unclear what is meant with "sufficient".	It is suggested to specify an approximate number or % of the total population to be studied.	Not agreed. Percentages or numbers of individuals cannot be defined as general rule but need to be decided on a case-by-case basis.
40-43	Please confirm that this is in Phase II studies.		Confirmed.
40-43	In heavily treatment-experienced populations women and ethnic minorities are under-represented and Phase 3 studies reflect the demography of the HIV epidemic. Therefore, should the guidance not acknowledge this difficulty by saying that the population studied should be consistent with the epidemiology of the population.		Currently the epidemic, globally as well as in Europe, is driven by patients from sub-Saharan Africa and south-east Asia, and the number of women is rather similar to that of men in that population. Furthermore, if e.g. there is a signal in exploratory studies indicating differential safety and/or efficacy e.g. in relation to sex, this should be further investigated in the confirmatory studies. Thus patients enrolled should reflect this concern, not the epidemiological situation.
40	Including heavily pre-treated patients (defined as?)		Clarified.
45	Replace "Paediatric Rule" with "Paediatric Regulation" since this is more technically correct	….a paediatric investigational plan should be developed in accordance with the Paediatric Regulation.	Acknowledged.
46-48	It is indicated that data should be obtained in renal and hepatic impaired patients. However, it should be emphasized that such data can also be obtained from volunteers who might make the conduct of such studies		Acknowledged, replaced "patients" with "subjects".

	easier to enrol patients.		
51-56	Since immune activation has been shown to be an independent predictor of disease progression, even better than viral load, measures of immune activations should be included in future studies. Measure of immune activation may include absolute/percentage of CD38+/CD8+; or CD38+/CD4+ T cells.	Measure of immune activation should be included in this section of the guideline.	Not agreed. The relevance of the numerous markers of immune activation as surrogate markers for treatment outcome has not yet been proven, while this is surely the case for HIV-RNA. Hence, this is an issue for the scientific community, but nothing that can be included as a regulatory request as part of drug development. The current goal is to restore (and keep) levels of CD4+ T-cells, along with virological control.
52	Viral load and CD4+ t-cell counts have been generally accepted as surrogate markers for efficacy in studies with anti-retroviral agents (although they are "accepted" they are not very good surrogates?)		See above.
58-62	In some studies, patients with virological failure are permitted to "switch" treatments, revising background and adding on the experimental drug if originally randomized to comparator (see below). Since increases in viral load (and drops in CD4) usually precede progression to clinical AIDS defining conditions (ADCs), as patients might switch treatments prior to onset of ADCs, rates of ADCs may not be expected to show superiority of a new agent, even if viral suppression with the new agent is proven superior to comparator.	Mention that rates of ADCs may not be expected to show superiority in studies where patients can switch treatments based on viral load.	Agreed. This is correct and is meant to be covered by the current wording ("… efficacy according to clinical events would be expected only in specific situations as mentioned above").
57-62	Regarding clinical events, non-HIV related clinical events should also be considered, especially for new compounds such as CCR5 antagonists that may increase the risk for non-HIV		Acknowledged. Please refer to section 1.2.7

	related infectious events. Also, cardiovascular events and non AIDS defining cancers should be the focus of increased attention since these events are bound to be more frequent than AIDS-defining events in the future.		
60	should include “serious non-AIDS” events here, perhaps with specific examples e.g. myocardial infarction, non-AIDS malignancies etc		Acknowledged. Please refer to section 1.2.7
60-62	The following statement has been taken out from the previous guideline: "The CDC criteria of 1993, excluding CD4 T-cell count as a defining event are still considered applicable". It is deemed important to maintain this statement as CD4 cell changes are evaluated separately as a marker of efficacy and not all jurisdictions accept the CDC CD4 criteria as an AIDS defining event.	Keep the following statement in the revised guideline: *"The CDC criteria of 1993, excluding CD4 T-cell count as a defining event are still considered applicable".*	Acknowledged, text reinserted.
60-62	“For compounds with potentially immunosuppressive properties, for example CCR5 antagonists…” There is no evidence from Phase 3 data with the CCR5 antagonist maraviroc that CCR5 antagonists are immunosuppressive. Clinical data showed maraviroc+OBT to increase CD4 cell counts several times more than patients receiving placebo+OBT and in a Phase 3 treatment naïve trial patients receiving maraviroc had improved CD4 cell counts compared with patients receiving efavirenz. There was also no evidence of an imbalance of adverse events where	It is suggested to either remove the reference to CCR5 antagonists or, if this reference to this class of compounds is to be retained, then it is suggested that the word “immnosuppressive” is replaced by “immunomodulatory”.	Not agreed. The text states *potentially* immune-suppressive compounds.

	immunosuppression might play a role.		
64	Specify that the statement relates to ”plasma HIV RNA”	For most efficacy studies, HIV plasma RNA is an appropriate measure of efficacy.	Acknowledged, text added.
1.2.2	Viral load assay comment; Unless the study is addressing drug activity against HIV-2 (a different virus to HIV-1), I don’t see the relevance of mentioning VL assays to detect HIV-2. With regard to ability to detect HIV-1 subtypes, this should be a universal requirement, not just in defined geographical areas		Acknowledged. Refer to 1.1, 1.2.2 and 4.3.4.
66-67	“In order to define the relationship between viral kinetics and sustained viral response, it is recommended that the dynamics of the early viral response are carefully documented, not only in dose finding studies, but also in confirmatory (sub) studies.” Further clarification is requested on precisely what regulators mean by this text and their expectations of Sponsors.		Acknowledged. Text removed; week 4 measurement (which is part of normal treatment guidelines) considered sufficient in late studies, since an early rapid decay rate per se so far has not been proven to be associated with improved long term outcome.
67-68	Lot of emphasis in early viral response. However no data to support clinical relevance of faster viral decay.		Acknowledged, see above.
69-72	The definition of “undetectable” should be more explicit. <50 copies/mL should be specified.	Undetectable HIV plasma RNA (< 50 copies/ml) is the preferred primary efficacy end-point…..	Acknowledged, text added.
70	Including time averaged change from baseline and time to loss of virological response (defined as?)		Acknowledged, text added.
80	Immune function: It would be nice to have outcome presented by baseline CD4 strata but it might be more appropriate to stratify randomization		Refer to section 4.2

	on this criterion.		
90	Are TREC data really useful? As far as I am aware, no direct clinical relevance. I think immune activation deserves a mention here, as this is potentially the most important (and neglected) immunological therapeutic target. Perhaps also mention IL-6 and D-dimer, these being the biomarkers that came out of SMART.		Acknowledged, and text is deleted. This paragraph refers to a field not really covered by this guideline, and scientific advice should be sought. The relevance of the numerous markers of immune activation as surrogate markers for treatment outcome has not yet been proven, while this is surely the case for HIV-RNA. Hence, this is an issue for the scientific community, but nothing that can be included as a regulatory request as part of drug development.
96	Baseline resistance testing is "recommended".	Baseline resistance testing should be mandatory in trials of antiretroviral naïve an antiretroviral experienced patients. This is good clinical practice already in "real life":	Acknowledged.
97	The reference that the resistance pattern should be documented at baseline should not be mandatory and only conducted if possible.	It is recommended that the resistance pattern should be documented at baseline if possible…….	Not agreed. Resistance testing prior to first therapy is now recommended in most clinical guidelines. In clinical studies, early as well as confirmatory, there is no reason to avoid resistance testing in patients with detectable viral load.
1.2.4	Tropism testing should become more relevant at time of failure on all drug regimens (not just R5 antagonists), since it is part of the analysis which determines the drugs still active against viruses in such patients. After all, that's which standard resistance tests are undertaken at time of failure		Acknowledged, tropism testing is of relevance for the construction of OBT and not only in case of treatment with some entry inhibitors. .
1.2.4	Resistance test data from clinical trials is the major source of data to inform resistance algorithms (which mutations mean what?). Thus, a statement should be made that resistance data from trials should be made publicly available, so that independent groups can develop algorithms based on pooled data.		Not agreed. This issue will need to be discussed further. At this stage it is premature to include such a statement in this guideline.
1.2.4	Viral fitness- why measure? There is		Not agreed. There is a clinical interest. Mutation 184V

	little evidence of a real impact on outcome.		is one clinical example. Furthermore, it is of interest to know if mutations are likely to be seen in patients off therapy.
99	Should we now mandate minority species resistance testing at baseline? Powerful data predicting outcome		Not agreed. This field is still too premature to be included in a regulatory guideline.
102-103	Species should be defined	It is suggested to add to the sentence lines 102-103: *"viral quasi species, that evolve due to selection and adaptation"*	Not agreed.
105-106	Integrase inhibitors should be added here, since sequential use of these new agents will need to be investigated.	The sentence in lines 105-106 should be re-worded to read: *"Essentially this refers to compounds within the same class of drugs such as PI, N(N)RTI, entry inhibitors or* ***integrase inhibitors****."*	There is no need to go beyond "same class" and to list the various classes. Text revised.
109-111	The clinical development programme should aim to identify resistance-associated mutations and clinical cut-offs that relate to clinical outcome.	The end of the sentence in lines 109-11 should be rephrased to read: *"...mutations and characterize in-vitro dose response curves, as well as providing clinical outcome data that help to establish clinical cut-off."*	Acknowledged.
111-113	The guidance is written with the expectation that viral resistance data is/can be collected from expanded access programs (EAP). The guidance should be written to reflect that EAP studies usually only allow the collection of limited serious adverse reactions.		The NfG is written in order to encourage pre-planned collection of resistance data also within the EAP.
111-113	It is suggested not including EAP in this sentence. It is very difficult to routinely collect resistance data in an EAP. Moreover this is not the purpose of such studies and we are not aware of any EAP which has routinely collected resistance data.	It is suggested to re-word the sentence in lines 111-113 as follows: *"Resistance data collected during long-term follow-up of clinical studies should normally be provided as yearly updates."*	See above.

112	Expanded Access Programmes (EAPs) are usually streamlined studies collecting only key required safety data; collection of samples for resistance testing may overly complicate these making it difficult for some treatment sites to participate. Most resistance testing comes from the pivotal registration studies.		See above...
112-113	Expanded Access Programs may not necessarily become available in advance of the approval of all future HIV medicinal products, since this will depend on the medical need.	….and patients treated in Expanded Access (EAP) if conducted should normally be provided as yearly updates.	See above.
114-116	CHMP should provide more clarity on expectations regarding the use of new external assays.		Text slightly changed. Such issues should be discussed with the Agency well in advance of a possible approval.
114-116	More clarity on EMEA expectations with respect to the use of new external assays is required.		See above.
117	When it appears "Genotype or Phenotype....." I do believe that should read " Genotype should be provided and phenotype could add additional information....." but not either one or the other. Phenotype in Europe is not available and would not be available in the near future, it is extremely expensive in comparison to genotype and no trial has confirmed yet its superiority to the genotype.		Agreed that phenotypic assays are rarely used in Europe. However, for some compounds (for instance CCR5-inhibitors) there is no genotypic assay available.
127	In line 127 it is suggested to replace “as regards” by “with regard to”		Corrected.
128	Please define or explain what is meant by “mechanistically”.		Text slightly revised.

129	Use “pharmacogenomics” instead of “pharmacogenetics”	In line 129 it is suggested to replace “pharmacogenetics” with “pharmacogenomics”	Acknowledged, heading amended.
129-133	It is unclear what is being looked for. Please clarify what to look for, at what time point to look for it, what triggers it and what materials do we need prospectively.		Acknowledged. The revised paragraph refers to pharmacogenomics and not immunogenomics, the latter being of scientific interest, but too complicated as part of drug development at this stage.
131	Therefore, genetic evaluations that elucidate the relationship between a test substance and inter-individual differences, [….] are encouraged.		See above.
134	Genetic host factors influence the natural course of HIV disease	Then add “as well as the adverse effect profile to some drugs” (?)	See above.
135	In line 135 it is suggested to replace “crucial” by “critical”		Acknowledged.
135-137	Long-term post marketing studies are often of necessity single-arm, non-comparative studies (as the experimental drug will have been approved). Although we agree long-term safety follow up is essential, interpretation of this data may be difficult due to lack of an internal comparator arm.		That is why sponsorship of cohort studies (like D:A:D) is of importance. Signals found in long-term (single-arm) studies can be further evaluated in such cohorts.
138-139	Safety issues that are related to a specific class of ARV, should be followed long-term for a new compound of the respective ARV class. In addition, any safety concerns for a new compound that may arise from pre-clinical and early clinical data should be followed carefully over the long-term.	It is suggested to re-phrase the sentence lines 138-139 to read: *“Safety issues related to a specific class of anti-retroviral, should be followed long-term for a new compound of this class. In addition, any safety concerns for a new compound that may arise from pre-clinical and early clinical data should be followed carefully over the long-term.”*	Wording slightly revised and includes further examples.
140	It there agreement on how to asses lipodystrophy? Should Dexascan be		Self-reporting would not be regarded as sufficiently sensitive. Sensitive and specific methods should be

	used in all studies? Is self-reporting of any interest? (Maybe if the trial is double-blinded).		used.
140	It is stated that "For example, lipodystrophy should be followed for PIs and NRTIs" Why not also NNRTIs when is already known that Efavirenz might be linked to lipoatrophy (ACTG 5142)?	Lipodystrophy should be followed for any antiretroviral.	Not agreed as a more excessive listing is not considered necessary.
146	In the sentence line 146 it is suggested to replace "sex" with "gender" and add "race"		"Sex" better reflects biological variation which is what is of interest (as opposed to social variation). "Ethnicity" is preferred compared to the term "race".
146-149	In the sentence line 146-149it is suggested to replace "justified Quality of Life instruments" with "validated Quality of Life instruments". It is also suggested to re-phrase and split up the sentence in two as follows: *"… double blind studies are encouraged. Incorporation of QOL instruments may provide…."*		Acknowledged, text amended.
MAIN GUIDELINE TEXT			
4.1.1	Test drugs against isolates of virus not only in PBMCs, but also macrophages. Important because PI transporter mechanisms, and nucleoside analogue phosphorylation patterns may be different between cell types		Not agreed. At this stage not of proven clinical relevance and cannot be considered a regulatory requirement.
202	Drugs should be tested against non-HIV viruses, where there is a potential antiviral activity. Examples come from HIV drugs also active against HBV and		Acknowledged that other virus should be studied, text added. Second paragraph of the comment not clear in this context.

	adefovir active against CMV as well. A statement need about the need to standardise the way that resistance test results are reported from trials i.e. proportion of all patients randomised with x mutation, as well as proportion of all pts with VL rebound/lack of suppression with x mutation		
204	In the sentence line 204 it is suggested to delete “normally”.		Not agreed.
207-208	It is suggested to re-word the sentence lines 207-208 to read: *“Pharmacokinetics of antiretrovirals may also be different in HIV-infected patients with advanced disease.”*		Acknowledged, text amended.
209	In the sentence line 209 it is suggested to delete “normally”.		Acknowledged, word deleted.
214	In the sentence line 214, it is suggested to replace “sex” with “gender” and add “race”		See above.
216	No clear relationships have been established between intracellular activated compound concentrations of NRTIs and efficacy/safety of the medicinal products. Also, these activated compounds are difficult to quantify with sufficient reliability. Therefore, it should not be requesting that for all drug-drug interaction studies with these medicinal products the intracellular triphosphate		Acknowledged, text added so that it should be done *as appropriate*.

	concentrations, including the variability of that, must be evaluated. This is particularly true if the medicinal product in development is not an NRTI itself, but if a drug-drug interaction study is performed with the medicinal product in clinical development and an existing NRTI.		
219	In the sentence line 219, it is suggested to replace “sex” with “gender”		See above.
220	In the sentence line 220 it is suggested to replace “activated” with “active metabolite”		Not agreed.
225	There is no relationship established between the intracellular pharmacokinetics of any antiretroviral medicinal compound (NRTI or any other class) and efficacy/safety. Also, there is no consensus on the validation of such concentrations and interpretation of intracellular concentrations (free, cell-bound) of antiretroviral medicinal products. Bridging between dose-regimens and formulations based on intracellular pharmacokinetics should therefore not be encouraged. At best, such investigations are explorative in nature and should not be used to derive any claims from.		Acknowledged, text revised.

231-233	The word "ideally" is too vague and we suggest changing the sentence to read as follows: For drugs whose pharmacodynamically linked parameter is C_{min} (trough), *it should be demonstrated that achievable and tolerable* mean *concentrations in vivo are several-fold higher than protein adjusted IC50/IC90 values for the full dose interval*		Partly acknowledged. Present wording is too vague and also potentially misleading. A much more comprehensive discussion focused on basic pharmacology including drug- target interaction would be needed and is not within the scope of a NfG (target affinity, rate of dissociation, relationship between ex vivo concentration vs. time profile and activity, etc.). Hence, instead of trying to expand, this sentence is removed.
238	TDM should also be done in patients with impaired drug metabolism (e.g., liver diseases, renal disorders).		Agreed, but this does not have to be included in text here. Please also refer to section 1.1
238-240	Compounds with a complex interaction profile and without a PK/PD relationship by definition do not require therapeutic drug monitoring. Only when a clear PK/PD relationship has been established and this range is within the clinically relevant range, therapeutic drug monitoring, theoretically, might be considered. The importance of a strong PK/PK relationship for safety and/or efficacy of the compound should be included in this text.		Not endorsed. Regardless of guideline text long term safety in patients with reduced clearance will always be quite limited – it will be based on the exposure seen in patients with normal clearance. Hence, a target level is welcomed for such patients, especially if the compound also has a problematic interaction profile.
238-40	Further clarification is requested on the possible role of therapeutic drug monitoring.		See above.
244	What is meant by "free" combinations should be clarified	In the sentence line 244 it is suggested to replace "free combinations" with "combination of two or three	Acknowledged, text amended.

		individual single-drug formulations…"	
254	With regard to the reference of new booster it seems to imply the two agents can be developed as a single entity – is this correct?	If the FDC includes a new anti-retroviral compound and/or a new "booster"……	As stated in the text.
270-272	The expectation should be clarified	It is suggested to re-phrase the sentence lines 270-272 to read: *"The applicant is therefore expected to provide a list of drugs and justification for specific drug-drug interaction studies of these selected drugs with the new compound. The rationale for these studies should include:"*	Acknowledged.
275-277	An indication is missing that, where good and acceptable theoretical rationale exists, based on absorption, metabolism and excretion on the novel agent, that interaction with a drug or class of drugs is very unlikely to occur, clinical interaction trials are not needed.		Please refer to first paragraph, stating that the studies should be done if mechanistically appropriate.
282	General reference to mycobacterial infections, but TB is so important that it deserves specific mention. This section is a little vague about what is required early, but I would have thought, given the global importance and the frequency of problems (and the value of a new drug free of interactions), that rifampicin interaction should be mandated as the highest priority at the very early stage.		See above.
283	Hyperlipidaemia, gastro-oesophageal reflux and therapies		Oral contraceptives included as early priority.

	used in the management of substance abuse. Propose to add: – drugs to treat pain syndromes, since they are used frequently in people with advanced disease. – oral contraceptives since use is recommended for women of childbearing age participating in clinical trials		
284	The sentence starting with "Within these areas…" should be clarified.	It is suggested to replace the sentence lines 284-285 with: *"It is recognized that drug-drug-interaction (DDI) studies cannot performed with all potential drugs that are authorized to use for a particular co-morbid conditions or co-infection. Therefore, DDI studies should be performed with essential and preferred drugs used in HIV-infected patient populations."*	Not agreed.
293	We concur with the EMEA's judgment that short term monotherapy is necessary to establish the activity of an antiviral compound and commend you for including it in this document.		Acknowledged.
294-337 354-357 518-524	Section 4.1.3 Monotherapy - Although monotherapy studies can provide important data regarding PK/PD relationships, it should be acknowledged that there might be circumstances where the potential risks of even short duration monotherapy outweigh the benefits. Certainly for known classes there may be settings where the risk of		Acknowledged. Resistance barrier has to be taken into account. However, new compounds of existing class nowadays often have a relatively high genetic barrier. New compound of new class should be studied in naïve patients for whom many alternatives exist, and resistance development might not be too dramatic, having in mind that these studies are performed in a low number of individuals.

	resistance development outweighs the benefit of collecting PK/PD data. This is especially important, but not limited, to NNRTIs which was already highlighted in the current applicable HIV Note for Guidance. In these cases, allowance should be made that monotherapy studies should not be required and further data can be obtained in combination studies instead prior to the initiation of confirmatory studies.		
295, 301	It would be helpful to provide more specific guidance on what is meant by “very brief period” and a “minimum” number of patients.	It is suggested for example to specify a two to three week-period.	Not implemented as it requires a case-by-case decision, however the text is slightly changed.
296	This is getting more controversial with the changing attitudes to early therapy. Also what we know about archived resistance. Perhaps these issues should be acknowledged, and some guidance provided on CD4 and VL thresholds that would indicate low rate of progression?		Not agreed. By keeping this sentence as it is, this recommendation will be possible to keep also in the future.
299	The document states that monotherapy studies should be as short as possible in duration – It would be helpful to give an example of how short. With viral loads measured every few hours it should be possible to establish an initial antiviral effect within 2-3 days. There may be some trade-off		See above.

	between sample size and length of the trial. With very short treatment periods (e.g. 2-3 days) there will probably be more variability in the response and thus somewhat larger numbers of patients might be needed. Although short periods of monotherapy cannot be avoided, the "tail" of low level drug exposure after stopping the drug for drugs with a long half life can be avoided by giving a period of potent combination therapy with short-half life drugs immediately on stopping the experimental drug. This may be worth noting as a possibility when the monotherapy studies are conducted in ART-naïve patients.		
299	"Monotherapy studies should be as short as possible in duration". This statement is too general. Two examples of current European trials of monotherapy with Darunavir/ritonavir of one year duration: Study Comparing Efficacy and Safety of Darunavir Boosted With Ritonavir to HART With 2 NRTI and Darunavir Boosted With Ritonavir in HIV-1 Infected Patient. ClinicalTrials.gov identifier NCT00421551 Treatment Simplification by Darunavir/Ritonavir 800/100 mg Once a Day Versus a Triple		See above.

	Combination Therapy With Darunavir/Ritonavir. ClinicalTrials.gov identifier NCT00458302 Risk of monotherapy depends critically on the drug tested. It is not the same for a boosted PI than for an NNRTI. Wording should be more specific.		
303	A specific cautionary statement should be added.	It is suggested to add the following sentence after the paragraph ending line 303: *"Specifically, patients with advanced AIDS, and or CD4 T cell counts <50 cells/mm^3 should excluded from dose-finding studies, monotherapy, or functional monotherapy. "*	Not agreed.
310-311	In the sentence lines 310-311 it is suggested to replace "data" with "results", and to replace "documentation" with "data".		Acknowledged, text revised.
312-313	In the sentence line 312-313 it is suggested to delete "it might be informative" and replace with *"....it may be helpful to conduct studies in healthy volunteers to define dosing, schedule, and exposure."*		Not agreed.
312	The data on the CCR5 antagonists, maraviroc and aplaviroc have shown that receptor saturation is NOT a good predictor of response, therefore it should be noted that this would not be expected for CCR5 antagonists.		Not agreed. Not a predictor of response, but (very) high saturation needed to achieve efficacy.
315	After paragraph ending line 315 it is suggested to add a clarifying		Correct for new compound/new class but not for new compound/existing class, where both naïve and

	sentence: *"It is expected that short-term monotherapy studies are performed in patients with fully susceptible HIV to the test compound."*		experienced patients might/should be studied.
316-317	Restriction of viral load limits at entry has not been encouraged as we have been encouraged to study patients with a wide range of baseline viral loads. Limitations of this kind in clinical trials would lead to restrictive labelling.		This refers to exploratory studies and restrictions make data easier to interpret.
321-323	PK/PD data usually are not available at this early stage or are only preliminary. It is not clear how viable this timing/approach is for HIV drug development.		The text says that modelling may be a helpful tool. Modelling is encouraged as part of drug development.
327-330	We suggest the following changes and additions: *The possible need for a loading dose and, in case of auto-induction, the need for dose adjustment over time should be considered* if the change in the relevant pharmacokinetic is such that the anticipated safety or efficacy is compromised. *If available PK/PD data and/or data related to the pharmacological class indicate that a parameter, e.g., Cmin, might be critical for anti-retroviral activity, the degree of and reasons for inter- and intra-individual variability in this*		First suggestion not acknowledged. This applies to the possibility of accurately estimate the drug efficacy during short-term monotherapy, therefore steady state PK conditions during the major part of the study is desirable. The second comment has partly been included but rephrased. Please also refer to comments lines 231-233.

	parameter should be specifically investigated. If, despite a review of relevant in vitro data and contributing intrinsic / extrinsic factor(s), no evidence-based explanation is available, the value of the target pharmacodynamically-linked parameter for efficacy (e.g., Cmin) can be adjusted such that a very high proportion of patients (e.g., >90%) can be expected to exceed that target value.		
331-334	This paragraph is controversial: 1) ACG5146 showed no benefit of optimising PI plasma levels with therapeutic drug monitoring compared to standard therapy. 2) In case of NRTIs, intracellular levels of active metabolites (nucleotide-triphosphates/diphosphates) are more important than plasma levels of parent drugs. Cellular activation rather than plasma concentration may play a greater role for uptake and metabolism of the parent drug at intracellular target. 3) Saturation and turnover of receptor targets, such as chemokine receptors may be more important than plasma concentrations of chemokine receptor antagonists.		TDM is not only something that would be used with regards to efficacy, but also safety. See comment regarding lines 238-240.
339-340	We suggest adding: (which include both marketed and/or experimental anti-retrovirals),		Not agreed.

	In order to explore tolerability and activity of the experimental compound in combination with other anti-retrovirals (which include both marketed and/or experimental anti-retrovirals), *further studies prior to the initiation of confirmatory studies may be indicated*		
339-342	Section 4.1.3 Combination studies - While an investigational regimen may not be appropriate for unstable symptomatic patients, many patients with CD4<200 who are clinically stable and meet inclusion/exclusion criteria may be appropriate for study inclusion. Guidelines should emphasize designing inclusion/exclusion to minimize risk to subjects but patients with CD4 <200 need not be excluded from all studies.		Not agreed. Naïve patients with compromised immune function should generally not be included in exploratory studies.
346-349	It is not clear to Sponsors how this sentence should be interpreted, especially for the development of new medicinal products intended for both treatment naive and treatment experienced populations. If completion of combination studies in treatment experienced populations is needed before progression into treatment naive patients then this will delay overall drug development cycle		Acknowledged, text clarified.

	timelines and prohibit the development of new medicinal products intended for treatment naive patients.		
349-352	Whilst we recognise the concerns that have been raised in patients receiving sub optimal regimens with low CD4 counts, this is exactly the population where the potential deficiencies of a new drug or too low a dose will show up best, so this difficulty should at least be acknowledged in the guidance.		Not agreed. Naïve patients with compromised immune function should generally not be included in early (still exploratory) studies.
350	CD4+ T-cell count below about 200: 200 is too high. 100 is more realistic.		See above.
350	It is suggested that 200 is too high and suggest <50 or <100.		See above.
350	"Symptomatic patients" is far too broad, as it would include everything from weight loss to night sweats to lymphadenopathy. We suggest replacing "symptomatic patients" to "**active AIDS-defining illnesses**".		See above.
350	It seems quite restrictive to exclude treatment naïve patients with a CD4 <200. In addition. The latest draft BHIVA HIV Treatment Guidelines recommend starting treatment with CD4 cell count <350; in this scenario, a large proportion of subjects will be excluded from future clinical studies.	Treatment naïve and/or symptomatic patients in need of immediate therapy under current HIV treatment guidelines should be included in exploratory studies only if there is a scientific rationale and if data are available from patients with less advanced disease.	See above.

	Therefore, a number for the CD4+ T-cell count should not be specified.		
350	According to the number of options available, the recommendation to treat early, the threshold of 200 CD4 seems too low to test new strategies in non-inferior designs. I would increase this threshold to 300 especially with new combination of investigational classes.		Not agreed. CD4 count of 200 seems a suitable compromise; it was many times confirmed that 200 cells is a relevant threshold for start of immune suppression.
351	A clearer wording than "exploratory" studies should be used as this might include Phase IIIb/IV trials where a restriction would not be relevant if the drug has already demonstrated safety and efficacy. If Phase IIb trials are meant here, it should be made clear.		Not endorsed. Throughout this document the references to “phases” is avoided on purpose and in alignment with guideline ICH E8, where the respective definitions can be found.
354-355	For treatment experienced patients the aim should be for 3 active drugs from at least two different classes.		Acknowledged.
359-361	Is this true? What is the basis for this statement? (Refers to: The dose regimens of the novel agent that are studied should not include any regimen that seem unlikely to be efficacious based on PK/PD predictions. These precautions should reduce the risk of selecting for HIV resistant to the novel agent.)		That a too low dose increases the risk for resistance development appears uncontroversial.

363-365	We are in total agreement with the agencies description and use of 'add-on' and 'substitution studies' and therefore suggest re-wording the first two sentences to emphasize those studies and delete reference to head-to-head comparison as follows: *The most commonly used designs in confirmatory studies* are *"add-on" or "substitution" studies*.		Not implemented as this follows in next sentence.
374-376	A good way to evaluate potential bias in non-inferiority study is to consider Per-Protocol as well as ITT population. Both populations should be pre-defined prior to lock of database. Proposal to add "The use of a per-protocol population as well as Intent-to-Treat population should be evaluated to minimize bias due to adherence record."		Not implemented as this is covered by general guidelines.
374-376	"…major efforts to document compliance" should be defined to provide clear guidance to Sponsors.		Acknowledged.
376	It is proposed that the statement be modified to highlight that both poor adherence and high drop out rates will bias results towards no difference.	As poor compliance <u>and high drop out rates</u> tend to bias	Acknowledged.
377-388	In confirmatory trials, patients on a comparator arm (e.g. OB alone) are often allowed to revise OB and add the new experimental drug after virological failure.	Discuss treatment "switch" or treatment "escape" study designs. If duration of treatment on the comparator arm ends up being substantially less than duration of treatment on the experimental drug arm, it may be appropriate to compare safety data based on exposure	Acknowledged, but to compare safety data based on exposure might dilute signals and bias data in favour of the experimental compound.

	Such treatment "switch" or "escape" is very important for the patient, allowing those randomized to the comparator arm to also benefit from the new treatment. However, such "switch" design may limit the duration of treatment on the comparator arm, making comparative safety evaluation difficult.	(e.g. events per 100 patient-years of exposure).	
384-386	It may not be in the best interest of the study to unblind the study and so, we suggest the following change: *In a study conducted in treatment naïve patients, for example, and depending on the magnitude of the observed difference in efficacy,* the protocol should prospectively define the time point at which virologic failure is defined and the patient is removed from the study.		Not agreed. If superior efficacy is clearly demonstrated in a study population where full viral suppression would be regarded as the relevant objective of therapy, it is questionable not to unblind treatment assignment for all individuals who have not achieved this objective.
391	Why? I don't understand what is meant here – if the study has been unblended then you should unblind individual is OK?		In order to obtain long term safety data, patients with full suppression should continue on assigned therapy.
391-392	"Long-term safety is a major concern which until now frequently has not been appropriately addressed in registration files." EMEA needs to balance their need/interest in long-term safety vs. early availability of life-saving HIV medicines (for which long term		The principles are acknowledged. Please refer to the section "4.4 Requirements for marketing authorisation", which is meant to balance early availability and risks associated with limitations in the safety data base.

	safety data might not be available). Long-term safety should still be positioned as a clear, post-approval commitment for these medicines.		
399	It is suggested to replace “sex” with “gender” and add “race”		See above.
400	It is worth giving in this document the acceptable threshold for non-inferiority.		In principle, the approach outlined in the guideline should be followed. Even though 10% often has been accepted, the reasoning behind the selected non-inferiority margin should be properly justified on a case-by-case basis.
407	In line 407 it is suggested to replace “as regards” by “with regard to”		Acknowledged.
416	High withdrawal rate should be clarified		Not agreed.
421	Need to expand to say that to undertake a PP analysis as well is important when assessing non-inferiority.		Not agreed. PP analyses should always be reported in non-inferiority analyses irrespective of treatment area.
425-426	Very conservative analyses (defined as?)		This mainly refers to patients withdrawn from therapy prior to study endpoint and may include counting withdrawal as failure in the experimental arm and to censor at time of withdrawal in the control arm. This clearly depends on the population, adverse reaction profiles, etc. The message is to discuss this in detail in the SAP.
427-428	It is suggested to replace “employ” with “be employed”, and to replace “dynamics” with “rapid changes”		Acknowledged.
428	Clarity should be provided on the term “Regulatory scientific		Text amended.

	advice" to ensure it accommodates national and/or CHMP scientific advice.		
431-432	Patients included in clinical trials should fulfil criteria that indicate a need to commence ART, as defined by recognised clinical guidelines. This means that one could never assess a strategy different from the currently recommended such as earlier treatment (at a higher CD4 cell count). It is absurd.		In most cases of drug development, for good reasons a new treatment strategy is not an integral part of the development programme. Text revised, however.
431-423	Patients included in clinical trials should fulfil criteria that indicate a need to commence ART, as defined by recognised clinical guidelines. ***Patients infected with resistant virus should not be regarded as treatment naïve and should not be included in these studies.***		Acknowledged. Please refer to section 1.2.4 and definition.
436-438	These studies are normally designed as substitution studies and the ***appropriate*** comparative agent should be chosen ~~so as to facilitate double-blinding,~~ taking into account pharmacokinetic interactions, pill burden (compliance), adverse effects, etc.		Acknowledged.
447	Subjects with resistant virus should not be included in treatment naïve studies. It is suggested to further clarify what "subjects with resistant virus"		Refer to section 1.2.4

	mean. Is one PI mutation sufficient or does this imply a primary mutation.		
447-449	Suggest the document indicate explicitly that resistance testing is warranted for studies of ART-naïve patients. However, would recommend that such studies exclude those patients with documented resistance ONLY to ART agents included in the study regimen. Resistance to other ART agents are not relevant (in the absence of cross resistance) and thus exclusion of these patients would be unnecessary.		Refer to section 1.2.4.
447-449	"…patient withdrawal due to other reasons than virological failure…" Further clarification would be helpful. For example: does this have **to be quantified or would a tabulation of reasons** other than virologic failure be sufficient?		Tabulation and a discussion would normally be sufficient. Major differences between treatment arms should be thoroughly evaluated.
447-449	Please clarify if this refers to viruses resistant to components in the study regimen; and, if so please change sentence to read: *Patients infected with resistant virus should not be regarded as treatment naïve and* <u>not be</u> *included in these studies.*		Refer to section 1.2.4
447-449	Comment should be provided regarding efficacy analysis of treatment-naïve subjects who, upon later genotypic analysis,		Refer to section 1.2.4

	enrolled with baseline resistance to one or more of the study drugs.		
454	Margin of non inferiority should be discussed for these studies. Since it is expected that the efficacy of the control arm in already suppressed patients is going to be very high (approximately 90% < 50 at one year), non-inferiority margin should be narrower than in trials of antiretroviral naïve patients were efficacy rates are closer to 75%;		Agreed, text revised. Expected benefits in terms of improved tolerability / toxicity have to be balanced against possible loss in efficacy. For that large, long-term studies are needed.
456-458	Studies of maintenance therapy with simplified and/or possibly better tolerated regimens in patients with HIV-RNA below the limit of detection after induction therapy is ***also***, ~~however,~~ an area of current clinical interest.		Acknowledged.
471-477	Among patients with controlled vial replication, at least 96 weeks (not 48 weeks) would seem appropriate to assess the primary endpoint. Also, it is of utmost importance that the power of the trial is appropriate as it will be a non-inferiority trial. Also the threshold for non-inferiority should be very strict as these patients are already controlled. It should be definitely below 10%, around 5 to 7%. Finally, it would seem important in these trials to provide information about nadir		See above.

	CD4 counts and peak viral load before the suppressive regimen.		
473	"…more than 48 weeks of follow-up…" Further clarification would be useful on the duration of longer-term follow up that would be expected.		See above
474-475	If safety is the primary endpoint you have to look for a specific measure or event. We suggest the following instead: *If improved safety is the rationale behind the experimental regimen, an adequate measure of safety should be defined in the protocol as* a key secondary endpoint		Acknowledged.
474-475	If improved safety is ***included as a main objective*** ~~the rationale behind~~ ***of*** the experimental regimen, an adequate measure of safety should be defined in the protocol as a co-primary end point.		Acknowledged.
481	You can't show response at baseline can you?		Acknowledged.
484-495	This paragraph has no mention of a placebo controlled study design and should include the option of an add-on placebo control if appropriate.		It is foreseen to be very rare with an add-on (4 regimen arm) versus a three regimen arm and placebo in this patient population.
490-492	A sensitivity score (usually GSS) requirement of >or = 2 for the OBR is considered appropriate. This makes it very difficult to perform superiority studies unless		The non-inferiority margin cannot be defined without knowledge of the expected activity of the active comparator on top of OBT. If the effect size cannot be estimated due to lack of data, a thorough discussion is needed and 10% could be acceptable if there are no

	these studies become very large to make a small difference also statistical significant. On the other hand, no strict guidance is given for the allowable difference in non-inferiority studies. This leaves the guidance very open and not clears what design is expected for confirmatory studies. It is suggested to specify more clearly the minimal difference to be demonstrated for 'add-on' studies and the margin of non-inferiority for 'substitution' studies.		safety disadvantages. A lead in, functional monotherapy phase with an active comparator is considered to be informative.
491	"For active comparator-controlled studies, the requirement for GSS ≥2 for the OBT…." should be replaced with "For active comparator-controlled studies, the requirement for GSS ≥1 for the OBT…."		Not agreed, especially not in this target population, with various treatment options remaining.
490-495	For active comparator-controlled studies, the requirement for GSS ≥2 in OBT may make the identification of an appropriate non-inferiority margin difficult.		See above.
494-495	The sentence "A brief period of active comparator controlled, functional monotherapy prior to optimising background therapy may be considered (see "Combination studies in section 4.1.3)" is vague. Is the EMEA encouraging or permitting a		"should be considered" means that the sponsor should take into account already available data, including those related resistance and the non-inferiority margin.

	monotherapy lead-in? Since that was encouraged in earlier phase trials, what is the purpose of doing it in Phase 3? Clarification is needed and provision should be given to allow justification by a company if this is not feasible.		
508	I think the document is saying that it will be possible to give marketing authorization to use a drug in patients with 1 or 0 remaining active drugs even though it is not recommended that trials are conducted in this group with so few options. If so, I agree with this and wonder if it could be spelled out more plainly; i.e. clear guidance not to do trials involving patients receiving < 2 active drugs – it is still possible to gain approval for use of the drug in such patients without doing such trials.		Agreed and this is sufficiently clear in the document
508	In patients with few or no remaining licensed therapeutic options, I do not agree with monotherapy studies. We should find other alternatives in these patients. The new drugs should not be tested initially in these patients. We should try to propose at least a combination of two new drugs for these patients, and a randomized trial might not be the only alternative. Well conducted one arm studies with the goal of reaching		Based on findings in previous studies short term monotherapy (for new compounds of existing class) should be possible to undertake in a safe manner also as part of confirmatory studies in this patient population.

	undetectable viral load should also be considered.		
508-548	This section is slightly confusing. Developmental stages-data packages should be more clearly distinguished from study designs. We propose the following adjustments.	This section refers to patients with no more than 2 likely active and possible to use licensed compounds based on sensitivity scores and treatment history. ~~Here drug development constitutes a challenge~~. In the interest of the patient, prolonged functional monotherapy must be avoided and, for the same reasons, the duration of dual active therapy should be minimised. Taking this into account, potential ***developmental scenarios and*** study designs ***may be as follows*** ~~include~~: ***Scenario A*** ~~1.~~If there are convincing data as regards the magnitude of the treatment effect and durability of response from comparative studies conducted in less heavily pre-treated patients, this may form the main basis for a submission. The rationale being that data derived from such studies delineates the efficacy potential for the compound as well as long-term safety under well-controlled conditions. ***To this data package studies are added which are conducted in the following target populations:*** ***1. Patients with at least 1 remaining licensed therapeutic option to be used in the OBT.*** For a novel compound from an existing class of drugs, short-term, functional monotherapy studies in the target population should be undertaken in order to assess the consequences of a wide spectrum of mutations on the anti-viral activity. For a compound belonging to a new class of drugs, functional monotherapy may provide reassurance as regards the anti-viral activity in the target population. Functional monotherapy should be followed by add-on treatment in patients likely to benefit from the experimental compound, with an OBT	The proposed revised wording is welcomed. Scenario A:1 should be restricted to patients with one (1) remaining licensed option.

		including at least one likely active compound. ***2. Patients with 2 remaining licensed therapeutic option to be used in the OBT.*** ~~For patients for whom it is possible to include two likely active licensed compounds in OBT, a~~ ***In such patients a*** placebo-controlled, add-on ***superiority*** study is an option. Time to virological response (i.e. usually defined as HIV RNA < 50 copies/ml) or sustained response at a pre-defined time point could be acceptable primary end points. After completion of the comparative phase, all patients may enter a long-term follow-up study in which they receive the experimental compound. After screening for inclusion, there will be patients detected who are ineligible for randomisation because they have less than two likely active licensed drugs available for use in OBT. These patients could be included in a parallel arm of the study in which they receive the novel agent plus OBT (which in some circumstances might include another experimental compound, ***see also below in scenario B***). Such patients should be followed in the same manner as those in the randomised arms of the study with the primary aim to provide safety data. An assessment of the new agent in this manner is considered to be preferable to inclusion of these patients only in extended access programs. ***Scenario B*** ~~3.~~ ***The developmental scenario includes*** ~~In~~ an organised co-development program ***of two companies***. To enable the use of two experimental compounds, putative pharmacokinetic interactions should have been investigated if mechanistically warranted. Factorial design may be used to document the efficacy and safety of two experimental compounds ***in the two target populations mentioned above (under Scenario***	

		A, 1 & 2). A minimum of 8 weeks of stable ART prior to initiation of functional monotherapy is needed to obtain interpretable results. The proper duration of functional monotherapy should be defined in relation to what is already known about the specific compound and the class of compounds. ~~To enable the use of two experimental compounds, putative pharmacokinetic interactions should have been investigated if mechanistically warranted.~~ If there are no specific safety or efficacy concerns, a submission based on 24-week study data is considered acceptable. Prior to the initiation of a development programme in this target population, EU regulatory advice is recommended.	
509-510	Given limited resistance assay sensitivity for NRTIs, the reluctance to use ENF, and the need for a viral tropism assay to assess the number of active agents available, not more 2 should not be specified here.	A more general wording, such as "very limited" or "few" is suggested.	Not implemented. It is agreeable that sensitivity scores are not a black and white phenomenon. However, with the present wording and design the idea of protecting study participants from inadequate therapy is the key message.
518-524	This emphasis on evaluating functional monotherapy is too much. What if a new drug cannot be used as monotherapy due to a low genetic barrier for resistance (e.g. 3TC)? Functional monotherapy could result in the development of resistance. Again, in traditional HIV drug development, monotherapy efficacy is demonstrated in Phase 1 and sometimes Phase 2 trials. Short-term efficacy should not need to be demonstrated again.		Refer to 1.2.4

523-524	This sentence suggests that functional monotherapy should always be a component of trials in this population. It is suggested to re-word the sentence in lines 523-524 to read: ***"If a short period of functional monotherapy is included,* it** should be followed by add-on treatment in patients…		Not agreed. With the revised NfG short term functional monotherapy (for compounds of existing class) is critical to make it possible to assess the resistance pattern of the drug.
524	See comment to line 354-355 the aim should be for new compound plus 2 active drugs. It is suggested to delete "likely" in line 524		Before the drug has been studied, likely is the word we can use. Text remains. However, the section has been clarified in accordance with another comment (see above).
525	Same comment as above: It is suggested to delete "likely" in line 525		Not agreed. Resistance is not a black and white phenomenon.
527-529	But not necessarily in this "failure" population?		Yes, also in this failing population.
530-537	Requirement of GSS/PSS score of at least 2 (2 active agents for OBT) in studies of patients with few/no remaining licensed treatment options would have made the conduct of some treatment-experienced studies highly problematic as GSS/PSS is likely <2 in ~50% in those randomized. Implementation of this approach would have resulted in such patients going on open label parallel arm, thereby losing the opportunity for randomized comparison. The risk of functional monotherapy		Not agreed that this is the problem. It is rather a problem that patients used to be allowed to be randomized to functional monotherapy to such a great extent. This guideline emphasises short term functional monotherapy (undertaken in a safe manner, section 1.2.4) in order to identify mutations affecting the activity of experimental compounds belonging to an existing class (but not new class).

	should be mitigated by the allowance of investigational compounds, in certain circumstances (and if drug-drug interaction data were supportive), to be used in OBT.		
532-534	It is suggested to add "or in a companion study" to the sentence lines 532-534: *"These patients could be included in a parallel arm of the study* ***or in a companion study*** *in which they receive the novel agent …"*		Acknowledged.
533-535	Is it reasonable to give functional monotherapy at all if there is only one possible active compound?		See above.
538-539	The sentence should be clarified. It is suggested to re-phrase the sentence lines 538-539 to read: *"In an organized co-development program* ***for 2 separate investigational agents****, factorial design may be …"*		Acknowledged.
545-546	Please clarify what are the minimum numbers of weeks of data required in patients with few or no remaining licensed therapeutic options at time of treatment failure.		Please refer to 4.4
Section 4.3.1	Please provide more clarity on age specific groups.		Not implemented. A guideline cannot be too prescriptive.
547	Clarity should be provided on the term Regulatory scientific advice to ensure it includes both national and CHMP scientific advice (see same comment above).		See above.

549 ff	Include a paragraph on „Studies in patients on substitution / maintenance therapy and drug users“since this is a large patient group and therefore need to be mentioned.		Not implemented. Interaction studies are considered sufficient. Please refer to 4.1.2.
556-557	Ideally, for a safe and well tolerated new agent designed to be used in treatment naive patients, the full range of children from very young to adolescents would be appropriate. However, especially for new agents designed to be used in treatment experienced patients, safety, tolerability or convenience may make use in the younger populations inappropriate. Thus, since virtually all neonates and infants have virus susceptible to well tolerated oral agents, it was not feasible to test an injectable agent designed to treat multi-drug resistant virus in the younger age groups.		Acknowledged.
575	In pregnant women more data on PK should be generated to assess PK in the pregnant woman, in cord blood, in milk		Acknowledged.
598	There are some evidences about the benefits of ART for HIV-HCV coinfected patients with cirrhosis. So coinfected patients with limited therapeutic options must be allowed to participate in clinical trials with new agents and in extended access programs.	… to long-term follow-up periods. Studies with new agents against HIV must include coinfected patients especially if they have limited therapeutic options. Extended access programs should not exclude coinfected patients.	Agreed, as already stated.

	They will be strongly benefited if they have a compensated liver cirrhosis		
599	Paragraph discussion for HBV co-infection: functional monotherapy of HBV in HIV-infected treated with combination antiretroviral therapy (cART) should be avoided. I.e., HIV-directed NRTI-backbone should include two HBA-active agents. If only one HBA-active agent is included in cART, another agent to treat HBV should be used, in addition to cART.		Acknowledged. Refer also to section 4.1.1.
607	The mentioned addition is considered important and is brought in line with the present activities for the extension of the CHMP antibacterial guideline with guidance on studies with new anti-TB agents.	Add paragraph at the end of section. ***In addition to the above mentioned viral co-infections, HIV –infected patients with active tuberculosis (TB) disease due to Mycobacterium tuberculosis constitute also an important, and in some study sites, large proportion of HIV-infected patients (commonly in advanced stage). Long and complex regimens and/or high pill burdens, additive toxicities and/or drug-drug interactions, can result in poor patient compliance, which may affect failure and relapse rates, transmission rates and the selection of resistant strains of HIV and M. tuberculosis. Therefore, sponsors may choose to include such patients in clinical studies along with TB-negative patients provided that treatment compliance and efficacy are not adversely affected by such factors in which case consideration should be given to pre-stratification by TB status.*** ***The assessment of safety of a new antiretroviral agent in patients with active TB disease is complicated due to the large number of medications that will need to be co-administered and the potentially extensive***	Not agreed. Studies with the power to compare the efficacy in TB patients (experimental vs. comparator) cannot be requested. Adequate interaction studies are what is expected from a regulatory point of view.

		range of drug-drug-interactions, which may change over time as HAART regimens are adjusted. The situation may become more complex in the case of treating patients with multi-drug-resistant (MDR-TB) and extensively resistant (XDR-TB) M. tuberculosis especially when experimental anti-TB agents are used. The possible occurrence of immune reconstitution syndrome is also a complicating factor for the overall safety assessment of these patients. Further detailed guidance on studies in this patient population are beyond the scope of this guideline. Recent relevant documents such as "addendum to the Note for Guidance on evaluation of medicinal products indicated for treatment of bacterial infections to specifically address the clinical development of new agents to treat disease due to mycobacterium tuberculosis" and documents that may have been issued by learned societies in the field of infectious diseases and clinical microbiology should also be consulted.	
608-633	Suggest to include specific references to conditional marketing authorisation (Regulation (EC) No 507/2006 and Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No. 507/2006) and possibility for accelerated assessment when detailing the requirements for marketing authorisation. The guidance on accelerated assessment should also be added under 3. Legal basis (161-190).		Not implemented. It is considered superfluous to refer to the possibility for "conditional approval" and "accelerated assessment" as specific regulatory guidelines covering these topics are available.

609	It is suggested to replace “as regards” with “with respect to” in line 599.		Acknowledged.
612	“Superior anti-retroviral efficacy” – Does CHMP mean statistical superiority? If, yes, then this should be clear in the guidance.		“Superior” / “superiority” in this document refers to a difference which is at least statistically significant
612	What is meant by “superior anti-retroviral efficacy” should be clarified If this means statistical superiority, then this should be made clear in the guidance.		See above.
612-616	These statements should be modified to reflect the current regulatory environment. Demonstration of superiority to current gold standard regimens is often not the goal or chosen statistical endpoint of Phase 3 studies with new agents in treatment naive patients. Many of these studies are designed to demonstrate non-inferiority to current anchor drugs either in an add-on or substitution design on a fixed backbone. We believe that if non-inferiority has been demonstrated together with an acceptable benefit risk (based on an improved tolerability profile to the existing anchor drug), it should remain an option that one-year safety and efficacy data should be considered as acceptable for marketing authorisation with 2 year data provided as a post approval		If the comparator is properly selected, major safety advantages cannot be demonstrated after one year. Therefore conditional approval based on improved safety seems not to be an option.

	commitment. Conditional authorisation should remain a procedural option for the agency in such circumstances. This change in the guidance would provide further incentives to the development of better tolerated agents in this patient population and facilitate earlier submission and registration of potentially important new agents to patients in the EU.		
616	The reference to “about 24 months” seems quite vague – this should be more clearly specified.		Clarified.
622-626	It should be further clarified what is meant by "several" vs. "few" remaining treatment options in determining study duration of 48 vs. 24 weeks.		Not agreed, text considered sufficiently clear.
650	Annual updating of resistance data may not be feasible. It is suggested to re-phrase the sentence line 650 to read: *“Resistance data should be updated on a yearly basis if not otherwise justified."*		This is how the text reads already.
Annex A	Presentation of drug-drug interaction data using a central tendency (geometric mean) with the range of observed data vs. the well-accepted 90% confidence interval for the change would be a step backwards in the design, reporting and clinical utility of pharmacokinetic data and make		It can be agreed that range may sometimes be misleading and the uncertainty in estimated variability will probably be large considering the often limited studies. It is therefore considered that measures of interpatient variability should not be included in the SPC but that this type of information could be included in the EPAR. The precision in the estimated geometric mean interaction effects i.e. the 90%CI is likely

	the results of many studies un-interpretable to scientists and clinicians and a disservice to patients. In the past, pharmacokinetic data, including drug-drug interaction results were unhelpful due to insufficient sample sizes and reporting of p-values that could not detect clinically relevant differences in drug exposures. Conversely, many studies have one or more outliers and/or spurious results that would negatively impact inappropriate analysis approaches, including presentation of the range of observed data. Application of bioequivalence testing methodology using a model-based approach to define the central tendency and confidence of observed changes is critical for interpretable and meaningful results. This approach is critical for a broad range of pharmacokinetic studies, including drug-drug interaction, food effect, dose-proportionality, pediatric dose finding vs. data in adults and has substantially improved the scientific and clinical applications of clinical pharmacology studies.		misinterpreted by many clinicians for being a measure of interpatient variability and thus should not be included in the SPC. It will have to be judged in the assessment of the data whether the interaction effect is estimated with sufficient certainty to be included in the SPC.
Annex A 7-8	This statement is vague. Please add: “Specifically, whether, in the		Not agreed, text considered sufficiently clear.

	presence of a coadministered agent, the dose of the anti-retroviral drug is unchanged or is to be modified to provide effective and safe exposure to each agent.”		
Annex A 9-12	We concur with this information and commend the EMEA for including this information. However, this item will involve discussion and the sponsor should avoid setting up and executing an a priori list without regulatory feedback.		Acknowledged, refer to section 4.1.2
Annex A 13-17	For anti-retroviral agents this will need to be expanded to discuss viral resistance testing and its use in that format. The role of compliance monitoring will need to be elaborated, particularly for those agents that have a narrow therapeutic index.		Not agreed, detail not considered necessary to specify in template A.
Annex A Table	The summary of interaction data should be indicated in an internationally accepted way by using the point estimate expressed as ratio (i.e. 1.35, and not increase of 35%). The variability around this estimate should be expressed by the 90% confidence interval of that point estimate, and not by the range. The 90% confidence interval provides a scientifically sound and widely accepted indication of the variability of the results. The range (min-max) is not		Partly acknowledged. GMR (only) to be presented in section 4.5. Details (variability) to be presented elsewhere in EPAR.

	informative and only provides information on (potential) outliers/extremes. By using the point estimate and the 90% confidence interval, all expressed as ratio, the guidance would be aligned with what is widely regarded as the standard method to express the results of drug-drug interaction studies. Prescribers are familiar with this way of summarizing interaction data and using this format reduces the risk of misinterpretation of the data in the SmPC.		
Annex A Table	If a physician would only refer to this part of the label when looking for the dosage to recommend when prescribing combination therapy, it is confusing if the dose used in the interaction study is mentioned here. As such medication errors can be triggered i.e. under dosing (efficacy issue) or overdosing (safety issue). - Interaction studies with the experimental drug may have been performed with lower dosages (when e.g. final selected dose/formulation was not yet available at the time the interaction study was performed). - Interaction studies with the experimental drug may have been performed with other, less		Acknowledged. The table has been revised to not include such details, which instead should be placed in the EPAR (Scientific discussion).

	bioavailable formulations so the dose used in the interaction studies may have been higher. Since in reality physicians do not always have the time to read the entire SPC, the fact that a physician will only check the interaction table is not unlikely. Therefore our suggestion would be not to require the information on the dose of the experimental drug used in the study. Instead of mentioning the dose of the experimental drug, it would be more useful to include the dose of the other drug for which the interaction is being assessed.		
Annex A Table	We would like to commend the agency for the well planned table found in Annex A with regards to the PK interactions in the SPC. This is very helpful.		Acknowledged.
Annex A Table	Drugs by therapeutic area: "*If a class of compounds is not affected, this is stated with a general comment."* It should be specified that we can use the literature to buttress / support the general comment.		No reference should be given in the table. Towards the Agency the applicant should always justify their statements, including the use of literature.
Annex A Table	Interaction: "*Negative findings are of interest – particularly within a therapeutic area where interactions are found for some compounds and not for others. "No interaction" then stated."* Define range of "no interaction"; may be specific for compounds		The range of "no interaction" will be different for every compound and substrate. Defining this is out of the scope of the guideline. This should be part of the evaluation of the study results and included in the study reports.

	or classes of compounds.		
Annex A Table	Interaction: "*The mechanism behind the interaction should be stated."* ...if it is known. How should support data be presented (in vivo, in vitro, etc, level of proof (hypothesis)?		Partly acknowledged. Only the mechanism should be stated in the SPC. Regards to support of data, refer to main document, including Legal Basis. Level of proof is judged during assessment of the data.
Annex A Table	"*INFECTION: Anti-fungals Fluconazole* *(HIV compound Y, x mg BID)"* This label needs to specify perpetrator / victim drug.		Acknowledged, example revised.
Annex A Table	"INFECTION: *Compound Y* *AUC 35 % (x-x)* *Compound Y Cmin 55 % (x-x)* *Fluconazole* *(CYP3A inhibition)"* Important inhibition of 2C9, 2C19 is not noted here		Acknowledged, example revised.
Annex A Table	Hyperlipidaemia: "*Based on theoretical considerations Compound Y is expected to increase simvastatin and lovastatin concentrations"* Which data? There are extant data.		Acknowledged, example revised.
Annex A Table	Hyperlipidaemia: "*Combination contra-indicated due to an increased risk of myopathy, including rhabdomyolysis"* There are data /recommendations that allow coadministration.		Acknowledged, example revised.
Annex A Table	Hyperlipidaemia: "*Interaction not studied, but not expected based on mechanistic*		If appropriate for the compound the statement can be suggested although it will be a matter of assessment.

	consideration" Does this statement mean that we can use this text in the EU?		
Annex A Table	Hyperlipidaemia: "*Preferred choice when coadministration with a HMG CoA reductase inhibitor is needed"* What is the dosing adjustment here?		Acknowledged, example revised.
Annex A Table	"Fluconazole": The increase or decrease indicated by an arrow symbol, and the corresponding CI, should be explained in footnote to ensure the consistency of the reporting in all DDI sections and across labels. E.g. "*Arrow up 35% is calculated by the Geometric Mean Ratio (GMR) of the test drug/ reference drug – 100%. The 90% for this number is derived from 90% CIs for GMR-100%		Acknowledged, example revised.
Annex B	Provision for inclusion of comparative safety information relevant to the physician should be given.		Not agreed. This Annex refers to how to present virology data.
Annex B 5	It is suggested to replace "as far as" with "if" in line 5		Not agreed.
Annex B 10-11	To what extent are all clades to be tested? Is there a clinical requirement to verify efficacy if in vitro testing shows a clade to be susceptible?		Refer to section 1.1
Annex B 12	Resistance: There is currently no opportunity		Such a summary (mean changes) is not considered important in the individual case, especially not with

	to summarize the mutations that can impact response or are selected by drug. Although footnotes in Table 1 and 3 assist they do not provide sufficient detail. More importantly, there is no opportunity to summarize the clinical isolate susceptibility data e.g. number and range of susceptible isolates from drug naive or isolates with resistance to class at baseline. I.e. Drug X had an median fold change/EC50 (range) against untreated clinical isolates and median fold change/EC50 (range) against resistant virus.		regard to phenotypic resistance, which is very seldom used in Europe.
Annex B 12	Recommend addition of key resistance mutations in vitro and/or in vivo within section 5.1. If such mutations were rarely observed among study subjects, there may be insufficient data but they would still merit a high-level summary in 5.1		Acknowledged.
Annex B 12	Resistance: There is currently no opportunity to summarize the mutations that can impact response or are selected by drug. Although footnotes in Table 1 and 3 assist they do not provide sufficient detail. More importantly, there is no opportunity to summarize the clinical isolate susceptibility data		Point taken on first paragraph. Second paragraph: such details are referred to "Scientific discussion" in EPAR, which contains request for such information in present Annex B. Not relevant for treating physicians.

	e.g. number and range of susceptible isolates from drug naive or isolates with resistance to class at baseline. i.e. Drug X had a median fold change/EC50 (range) against untreated clinical isolates and median fold change/EC50 (range) against resistant virus.		
Annex B 13	Text and TABLE 1: The table format is not necessary since the more clinically relevant information is included in Table 3. We would rather see text summary of the Phase II monotherapy data. Patients receiving functional monotherapy are becoming increasing difficult find – with the recent approval of new classes integrase and CCR5 inhibitors and next generation NNRTIs on the horizon – it is likely that this table will be derived from very limited data. If this Table is retained it is essential that both the range in log reduction and the number of patients is included, since limited numbers may bias outcome.		Not agreed. With the present revised guideline short term functional monotherapy (new drug existing class) will be a corner stone of assessing the activity of the drug by baseline resistance.
Annex B 16-18	Is a rationale required here to establish that a short-term monotherapy represents an adequate challenge to a drug's intrinsic anti-retroviral efficacy? In addition, we feel that the method for determining		Cannot be defined more clearly at present. Should be justified and also, as pointed out later “The cut-offs of activity used in TABLE 1 (previous page) should be specifically reflected upon in relation to the table 3.”

	resistance cut off values be described more clearly and in more detail.		
Annex B 16-18	Data should be derived from short term functional monotherapy studies. Suggest cross reference to Sec. on Monotherapy studies, line 293-337, esp. line 299 stating that duration of functional monotherapy should be as short as possible. Also, reference is made to 4 week data from patients with viral sensitivity score of 0. Suggest cross-reference to the non-randomized treatment for patients with GSS<2, lines 531-532.		Acknowledged.
Annex B 23	Number of mutations Need to consider mutations that potentially increase virological response (i.e. -ve scores) – hence scores for 'activity not affected' should be <X and not 0-X		Not agreed. This appears not to have been shown so far.
Annex B 25-27	"Codon" should be changed to either "Amino Acid Substitution" or Codon Change or similar.		Acknowledged.
Annex B Table 2	Provide n's in addition to %'s		Acknowledged.
Annex B 41	Table 3 The most clinically useful table especially with the control arm shown. Ideally we would like to see Phenotype included Table 3 could be broken down into Table 3a MAH mutation		Partly acknowledged. However phenotypic results should normally be looked for in the EPAR (not used in clinical practise in Europe).

<table>
<tr><td></td><td>score; Table 3b alternative score; Table 3c Phenotype & Response. Data could then be presented completely for each mutation rather than summarizing data. Shading could be used to highlight sensitive, reduced activity, resistant cut-offs.</td><td></td><td></td></tr>
<tr><td>Annex B
Table 3
42-43</td><td>Please change to:
Proportion (%) of patients with < 50 cps/mL at week X by genotypic or <u>phenotypic</u> sensitivity score in OBT and baseline resistance
Genotypic / <u>phenotypic</u> sensitivity score in OBT *</td><td></td><td>See above.</td></tr>
<tr><td>Annex B
51-54</td><td>Are there specific figures that would aid the reviewer?</td><td></td><td>They are provided (tables).</td></tr>
<tr><td>Annex B
56-58</td><td>Based upon which protein concentration? Is this affected by the intrinsic binding potential of the drug?</td><td></td><td>Comment unclear. The text seems to be adequate.</td></tr>
<tr><td>Annex B
59</td><td>Table: Activity against wild-type virus
In the current format this table is difficult to complete. Would like to see a table in the format shown in the next column – the advantage of this format is that it is sufficiently flexible that data on additional clinical isolates can easily be included e.g.4/R5, etc.</td><td>TABLE X. Activity Against Laboratory and Clinical Isolate Wild-type Víruses
<table>
<tr><th>Parameters</th><th>Median EC_{50} (nM)</th><th>Range (nM)</th><th>Median EC_{90} (nM)</th><th>Range (nM)</th></tr>
<tr><td colspan="5">Laboratory Virus Data [a]</td></tr>
<tr><td>HXB2 (n=X)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>BaL (n=X)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>IIIB (n=X)</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Serum Shift Data</td></tr>
<tr><td>50% Human Serum (n=3) [b]</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">Clinical Isolate Data</td></tr>
</table></td><td>Acknowledged.</td></tr>
</table>

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<table>
<tr><td>Subtype A (n=X)[c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype AE (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype B (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype C (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype D (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype F (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype G (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Subtype H (n=X) [c]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>HIV-2 (n=X) [d]</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CXCR4-utilizing (n=X)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>CCR5-utilizing (n=X)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>NNRTI Resistance Virus</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="5">a. cell line assay clinical isolate detail</td></tr>
</table>

Footnote should include type of assay – single cycle multi cycle etc
</td>
<td></td>
</tr>
<tr>
<td>Annex B
62</td>
<td>Detailed characterisation of mutant virus should also be included in certain circumstances e.g. NNRTIs
Option to include level of resistance conferred by individual resistance mutations</td>
<td></td>
<td>Comment unclear.</td>
</tr>
</table>

Annex B 63-64	Please add: Assay used for phenotypic resistance testing and type of cell lines used should be specified. **Fold change or other relevant parameter (i.e. maximal % inhibition)** according to accumulating resistance should be presented.		Acknowledged.
Annex B 68	Would like to see this broken into two sections i) BL resistance of clinical isolates to the drug in question ii) Cross resistance to other drugs following failure of the drug in question. Criteria for inclusion should be considered – should only include isolates that have developed a mutation and reduced susceptibility to the candidate drug – often if all failures are included the effect can be diluted		Acknowledged.