



1 19 September 2013
2 EMEA/CPMP/EWP/633/02; Rev 3
3 Committee for Medicinal Products for Human Use (CHMP)

4 **Guideline on the clinical development of medicinal**
5 **products for the treatment of HIV infection**
6 **Draft**

First draft	15 March 2012
Draft Agreed by IDWP	30 May 2013
Adoption by CHMP for release for consultation	19 September 2013
Start of public consultation	30 September 2013
End of consultation (deadline for comments)	31 March 2014

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8 This guideline replaces EMEA/CPMP/EWP/633/02 Rev 2

9
10 Comments should be provided using this [template](#). The completed comments form should be sent to IDWP.Secretariat@ema.europa.eu

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Keywords	<i>HIV, Antiretroviral, Drug development, Guidance</i>
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13 **products for the treatment of HIV infection**

14 **Table of contents**

15	Executive summary	4
16	1. Legal basis and relevant guidelines	4
17	2. Pharmacodynamics and pharmacokinetics	5
18	2.1. In-vitro virological studies	5
19	2.1.1. Initial laboratory evaluations.....	5
20	2.1.2. Evaluation of resistance in isolates obtained during the clinical programme.....	6
21	2.2. In-vivo pharmacokinetics	7
22	2.3. Drug-drug interactions	7
23	2.4. PK/PD considerations	7
24	3. Clinical efficacy.....	8
25	3.1. General considerations for development programmes	8
26	3.2. Efficacy endpoints	9
27	3.2.1. Virological endpoints	9
28	3.2.2. Immunological endpoints.....	9
29	3.2.3. Clinical endpoints	9
30	3.3. Dose finding studies	10
31	3.3.1. Monotherapy studies.....	10
32	3.3.2. Combination studies in treatment naive patients	10
33	3.3.3. Dose finding in patients with viral resistance relevant to the drug class to which the	
34	new agent belongs.....	10
35	3.4. Confirmatory studies	11
36	3.4.1. General considerations	11
37	3.4.2. Studies in treatment naive patients	11
38	3.4.3. Studies that include patients with viral resistance relevant to the drug class to which	
39	the new agent belongs	12
40	3.5. Fixed dose combination medicinal products	15
41	3.6. Studies in special patient populations.....	15
42	3.6.1. Studies in children	15
43	3.6.2. Studies in older patients.....	16
44	3.6.3. Studies in pregnant women	16
45	3.6.4. Studies in patients co-infected with hepatitis B or -C.....	16
46	3.6.5. Tuberculosis co-infection	17
47	3.6.6. HIV-2 infection.....	17

48	4. Clinical Safety	17
49	5. Information in the Summary of the Product Characteristics	17
50	6. References	18
51		

52 **Executive summary**

53 This document provides guidance on the clinical development of direct-acting antiretrovirals for the
54 treatment of HIV infection.

55 In contrast with the approach taken in EMEA/CPMP/EWP/633/02 Rev2 this revision defines trial
56 populations according to documented viral resistance rather than treatment histories. In this guidance
57 document, the term *treatment naïve* refers to patients who have not previously received antiretroviral
58 therapy, and who are infected with HIV without mutations conferring drug resistance in their major
59 viral populations, as determined by standard genotypic assays (i.e. virus that is predicted to be fully
60 susceptible). The term *treatment experienced* is not used in this revision since it does not adequately
61 define a patient population that is harbouring drug-resistant viruses. Instead, the focus is on the
62 evaluation of the in-vitro and in-vivo activity of a new agent against HIV, including virus with
63 demonstrated resistance that is relevant to the class to which the new agent belongs.

64 In EMEA/CPMP/EWP/633/02 Rev 2 it was recommended that placebo-controlled studies with a
65 statistical superiority design and with virological endpoints at 24-48 weeks should be performed in
66 patients who were failing on their treatment regimen in order to obtain an indication for use in
67 “treatment experienced” patients. However, due to the introduction of numerous new antiretroviral
68 agents in recent years, and to the general use of pharmacoenhancement (“ritonavir-boosting”) when
69 protease inhibitors are part of the treatment regimen, the development of extensive resistance *de*
70 *novo* is now rare in patients who are treated with optimised regimens in the EU. As a result, placebo-
71 controlled superiority designs are no longer feasible and non-inferiority trials in such populations are
72 fraught with methodological problems.

73 Therefore for all new agents, it is proposed that data on safety and efficacy are generated in
74 randomised double-blind controlled trials in treatment naïve patients. For first agents of a new class
75 and in the absence of any known cross resistance to the new class, such data might suffice for an
76 indication encompassing all HIV-infected patients. Additional data would be required to support the use
77 of new agents of existing classes in patients infected with virus with resistance to other members of
78 the class to which the new agent belongs. In this setting data should be generated from one or more
79 studies that include a short initial period during which patients continue their failing regimen with or
80 without addition of the new agent (which may itself be given at different dose regimens) followed by a
81 longer period during which all patients are treated with the new agent (at one or more dose regimens)
82 in association with an optimised background regimen.

83 Development programmes for new agents that are not suitable for study in treatment-naïve patients
84 (e.g. injectable agents) would need to be discussed on a case by case basis.

85 In line with this approach it is recommended that the antiviral activity, specificity and capacity for
86 selection of resistant variants initially be characterised *in vitro*, and that all viral isolates from patients
87 failing therapy be characterised genotypically as well as phenotypically if not previously investigated.
88 This revision recommends that drug-drug interaction studies that seem to be the most crucial for the
89 safe and effective use of a new agent are performed prior to marketing authorisation.

90 Suggestions for how the data generated in the clinical program should be reflected in the SmPC follow
91 at the end of the guideline.

92 **1. Legal basis and relevant guidelines**

93 This guideline has to be read in conjunction with the introduction and general principles and parts I
94 and II of the Annex I to Directive 2001/83/EC as 2003/63/EC of 25 June 2003 amending Directive

- 95 2001/83/EC Applicants should also refer to other relevant European and ICH guidelines (in their
96 current version) on the conduct of clinical development.
- 97 • Choice of a Non-Inferiority Margin - CPMP/EWP/2158/99
 - 98 • Pharmacokinetic studies in man – CHMP/EWP/147013/04
 - 99 • Investigation of drug interactions – CPMP/EWP/560/95
 - 100 • Use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal
101 products - EMA/CHMP/37646/2009
 - 102 • Evaluation of the pharmacokinetics of medicinal products in patients with impaired hepatic
103 function - CPMP/EWP/2339/02
 - 104 • Evaluation of the pharmacokinetics of medicinal products in patients with impaired renal
105 function - CPMP/EWP/225/02
 - 106 • Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06
 - 107 • Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99
108 (ICH11)
 - 109 • Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population
110 CHMP/EWP/147013/04
 - 111 • Fixed Combination Medicinal Products CPMP/EWP/240/95
 - 112 • Guideline of the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation
113 data EMEA/CHMP/3133666/2005.

114 **2. Pharmacodynamics and pharmacokinetics**

115 **2.1. *In-vitro virological studies***

116 **2.1.1. Initial laboratory evaluations**

117 The in-vitro investigation of a new agent for the treatment of HIV should, as a minimum, include the
118 following:

- 119
- 120 1. Characterization of the mechanism of action of the new agent
 - 121 2. Determination of the antiviral activity in cell culture, including the determination of
122 EC50/90 against HIV-1 and HIV-2 and against a relevant range of HIV subtypes, laboratory
123 strains and clinical isolates. It is recommended that cell lines include peripheral blood
124 mononuclear cells (PBMCs).
 - 125 3. Determination of the impact of protein binding on EC50/90.
 - 126 4. Determination of the cytotoxicity and of the therapeutic index of the drug against the same
127 cell line in which antiviral activity is determined.
 - 128 5. Assessment of the in-vitro selection of resistant variants and characterisation of their
129 phenotypic and genotypic properties. Selection experiments should be performed with a
130 range of drug concentrations in relation to the EC50, to characterize the concentration-
131 dependency of the selection of resistant variants.
-

- 132 6. Characterization of the activity of the new agent against viruses (which may include
133 laboratory derived recombinants) harbouring a range of resistance associated mutations
134 (RAMs). Studies should adequately describe the potential for cross-resistance between the
135 new agent and licensed antiretroviral agents.
- 136 7. Studies of the potential for additive/synergistic or antagonistic effects to occur when the
137 new agent is co-administered with other antiretroviral agents.
- 138 8. Studies of the activity of the new drug against other viruses (e.g. in particular Hepatitis B
139 and C viruses). If activity that might exert selective pressure against such viruses is
140 detected, this should prompt further investigations to evaluate the potential for this to
141 occur when using the agent to treat HIV in co-infected patients.
- 142 9. If the new agent requires intracellular modification to form the active moiety (e.g. serial
143 phosphorylation as for NRTIs) it is important to assess the possible effects of co-incubation
144 with other drugs that may compete for the activation pathway resulting in modification of
145 antiviral activity. The results of such studies may be particularly helpful should any
146 unexpected findings arise when using certain regimens during clinical studies or in routine
147 clinical care.

148 **2.1.2. Evaluation of resistance in isolates obtained during the clinical** 149 **programme**

150 Throughout the clinical programme it is expected that baseline isolates and all isolates obtained from
151 those who fail treatment (as defined per protocol) that are present in sufficient quantities should be
152 subjected to phenotypic and genotypic investigations. The IAS-USA list of mutations is a suitable
153 reference (<https://www.iasusa.org/sites/default/files/tam/19-4-156.pdf>). Although single such
154 mutations at baseline might have a very low impact on the virological response to treatment, their
155 presence may indicate prior exposure of the virus to antiretroviral agents and enhance the risk of
156 emergence of more resistant variants.

157 The choice of assays and assay conditions should be justified. Since phenotypic assays are hardly used
158 in clinical practice, the focus should be on generating genotypic data. Phenotypic analysis should be
159 performed, however, on clinical samples from patients failing without previously characterised
160 genotypic changes. The results should be reflected in the SmPC and the correlation between genotype
161 and any relevant phenotypic resistance should be described. For genotypic assays population
162 sequencing of the major viral population remains the recommended approach. Monitoring of changes
163 in minority variants using next generation sequencing techniques may be useful within the drug
164 development program but is presently not applicable for clinical practice. In development of CCR5-
165 inhibitors the use of genotypic assays in combination with software algorithms in clinical studies is now
166 accepted, in line with European expert consensus (1)

167 If new assays are used in clinical trials and are needed to identify patients suitable for treatment
168 and/or to monitor treatment effects, the availability of these assays or validated alternatives outside of
169 the clinical study setting should be addressed and discussed with EU Regulators well in advance of a
170 MAA.

171 All genotypic changes that emerge during treatment should be assumed to be associated with the
172 selection of resistant variants, unless otherwise proven through phenotypic analysis. In all studies the
173 documentation of emergent resistance against the new agent and against the other components of the
174 regimen should be tabulated.

175 When evaluating the short term viral response in patients infected with multiple drug resistant viruses

176 the use of clonal or next generation sequencing techniques with frequent sampling should be
177 considered. The results may add to the understanding of viral dynamics and may be useful when
178 assessing any correlation there may be between results in the early, comparative phase of the study
179 and the subsequent prospective observational phase. These techniques are evolving very quickly;
180 hence, a standard method for use cannot be recommended. Therefore, even when the protocol
181 includes use of a recently developed sequencing method it is recommended that samples should be
182 collected during clinical studies so that retrospective analysis using future technological advances is
183 possible.

184 **2.2. *In-vivo pharmacokinetics***

185 The pharmacokinetic study programme should follow the relevant guidelines (Pharmacokinetic studies
186 in man – CHMP/EWP/147013/04). In order to reduce the risks associated with sub-optimal therapy in
187 the HIV-infected individual, the initial pharmacokinetic studies should be performed in healthy, HIV-
188 negative volunteers. Studies of pharmacokinetics in patients with hepatic and renal impairment should
189 usually be performed prior to approval, and should be conducted in accordance with the principles
190 described in the relevant CHMP guidelines (CPMP/EWP/2339/02 and CPMP/EWP/225/02).

191 The determination of drug concentrations in cerebrospinal fluid and genital secretions should be
192 considered, though the impact on therapeutic (or prophylactic) decisions is presently unclear.

193 **2.3. *Drug-drug interactions***

194 Due to the requisite for treatment of HIV with combination regimens and the high likelihood that
195 patients will be taking a range of other medications there is a major potential for clinically relevant
196 drug-drug interactions to occur. In addition, many types of antiretroviral agents have a considerable
197 potential to be involved in DDIs (as perpetrator and/or as victim), which complicates the assembly of
198 HIV regimens and the management of concomitant medical conditions. Therefore it is essential that
199 existing CHMP guidance is consulted (Investigation of drug interactions CPMP/EWP/560/95 Rev 1) and
200 that sufficient investigations are conducted in the initial pre-approval period to support the co-
201 administrations anticipated in the clinical studies and in clinical practice.

202 It is not expected that all the drug-drug interaction studies considered to be appropriate or at least
203 desirable will have been performed at the time of initial licensure. In the initial development
204 programme it is recommended that priority should be given to DDI studies with other drugs for the
205 treatment of HIV and for the treatment of concomitant infections (e.g. HCV, HBV, invasive fungal and
206 bacterial infections including mycobacterial diseases), hormonal contraceptives, drugs for the
207 treatment of metabolic abnormalities such as hyperlipidaemia, gastro-oesophageal reflux and drugs
208 used in the management of substance dependence. Within these areas, drugs without reasonable
209 therapeutic alternatives and with a potential for interaction should be prioritized for study. The initial
210 dossier should include a plan for completion of the interaction study programme.

211 **2.4. *PK/PD considerations***

212 Data derived from the initial studies in healthy subjects may be used for the preliminary selection of
213 doses and regimens likely to be effective and tolerable in HIV-infected patients. For example, plasma
214 levels may be compared to protein binding adjusted EC₅₀/95 values for target viruses, to justify target
215 pharmacokinetic indices and the range of doses to be tried in patients with HIV infection.

216 It is essential that the relationship between drug exposure and safety and efficacy parameters is
217 adequately explored based on data obtained from clinical studies in HIV-infected subjects. Therefore

218 adequate PK sampling should be planned including intensive sampling in subsets of patients. Factors
219 that may impact on drug exposures should be explored by means of population PK analyses. The
220 results of PK/PD analyses should be taken into account when assessing the potential clinical relevance
221 of any alterations in drug exposures that are observed in studies in subjects with hepatic or renal
222 insufficiency and in DDI studies.

223 **3. Clinical efficacy**

224 ***3.1. General considerations for development programmes***

225 The range of licensed antiretroviral agents commonly allows construction of fully active (generally 3-
226 active drugs with or without a pharmacokinetic enhancer) combination regimens even in patients that
227 have repeatedly failed prior therapy or do not tolerate specific agents. Thus, therapeutic failure is
228 becoming increasingly less frequent and is usually due to poor adherence rather than to insufficient
229 inherent activity of the regimen.

230 As a result, it is no longer generally thought feasible to demonstrate superiority in studies in which
231 patients who are failing their current regimen are randomised to receive a new agent or placebo added
232 to optimised background regimens. In addition, the efficacy of the optimised background regimens is
233 such that a non-inferiority study design might not provide adequate assay sensitivity. Furthermore,
234 recruitment has been difficult during recent attempts to conduct non-inferiority studies in treatment
235 experienced patients with existing treatment options, especially when there are protocol-specified
236 limitations to the background regimen.

237 As discussed in more detail in section 3.3, there is a need to reconsider the content of clinical
238 development programmes according to the properties of each new agent. To summarise:

239 *For a new agent of a new class* randomised controlled double-blind studies in patients with fully
240 drug susceptible HIV (referred to as treatment-naïve patients for the purposes of the following
241 text, although it is acknowledged that drug-resistant virus may be acquired through transmission)
242 might suffice to support use in HIV-infected subjects regardless of prior treatment history and
243 presence of RAMs relevant for agents of other classes.

244 *For a new agent of an existing class* it is also proposed that randomised controlled double-blind
245 studies are conducted in treatment naïve patients to provide the basic evidence that the selected
246 dose regimen is suitably efficacious and has an acceptable safety profile when compared with
247 appropriate widely-recommended regimens. This could suffice if a claim is to be made only for
248 use in class-naïve patients. However, an endorsement for use in patients infected with virus that
249 is resistant to some or all of the other agents that are in the same class as the new agent would
250 require additional clinical evidence of efficacy.

251 The following sections provide further details of efficacy endpoints and the clinical study designs that
252 are suggested in each of these scenarios.

253 Finally, it is possible that a drug of an existing or new class might be developed only for patients with
254 extensively drug resistant virus (e.g. this could apply for agents that would not be suitable for use in
255 other patient populations due to an injectable route of administration or need for a complex dosing
256 regimen, or perhaps due to safety considerations). Specific recommendations for development of such
257 agents are not included below and it is recommended that each case is discussed with EU Regulators to
258 identify suitable development strategies.

259 Section 5 of this guidance provides examples of how the final indications resulting from these
260 programmes could be worded as well as issues for other sections of the SmPC.

261 **3.2. Efficacy endpoints**

262 **3.2.1. Virological endpoints**

263 The suppression of HIV replication is an established surrogate endpoint for clinical benefit, maintained
264 immune status and durability of the virological response by preventing the selection of resistant
265 variants. It is expected that plasma HIV-RNA be quantified using a validated real-time PCR method.
266 The use of a validated and sensitive assay for plasma HIV RNA that meets current standards is
267 essential.

268 In early dose-finding studies using short-term monotherapy, and when studying short term addition of
269 a new agent to a failing regimen in patients harbouring virus with resistance relevant to the class to
270 which the new agent belongs (see below), the mean change from baseline in HIV-RNA would be the
271 primary end point.

272 In all other clinical studies the proportion of subjects that achieves and maintains suppression of the
273 plasma viral load to below the limit of quantification (<LLOQ of the HIV-RNA assay used) is the
274 preferred primary efficacy outcome measure. Detectable low level viraemia (i.e. above the LLOQ for
275 the assays with the lowest LLOQ in clinical use, but below a previously applied cut-off such as 50 or
276 400 copies/mL) could indicate real differences in antiviral potency between regimens. Since future
277 comparative trials are expected to be of non-inferiority designs, the most sensitive virological endpoint
278 possible (i.e. < LLOQ of a suitable assay) should be used.

279 The use of the FDA snapshot algorithm with missing, switch or discontinuation = failure, is considered
280 appropriate (2), but should be complemented with a secondary Time to Loss of Virological Response
281 TLOVR analysis based on a confirmatory measure of viral load.

282 In addition to the proportion of patients reaching the <LLOQ endpoint the proportions with viral loads
283 falling into pre-defined strata (e.g. 20-49, 50-99, 100-199, 200-400 and > 400 copies/mL) should be
284 tabulated.

285 There is presently no clinical consensus on when to switch treatment in case of persistence or re-
286 appearance of detectable low level viraemia and such patients are managed on an individual basis.
287 Therefore protocol-specified criteria that would be applied to serial viral load measurements to prompt
288 a change in therapy may be based on viral loads above the LLOQ. The protocol defined criteria for
289 changing therapy should be justified in relation to the known qualities of the study drugs (primarily the
290 risk of selecting for resistance to one or more agents within the regimen) and to relevant clinical
291 treatment guidelines.

292 Taking the considerations above into account, virological failure, whether primary or secondary, should
293 be clearly defined in the protocol and the definition should be carefully justified based on the assay and
294 the criteria that will be applied to trigger a switch in treatment.

295 **3.2.2. Immunological endpoints**

296 Effects on absolute CD4+ T-cell count, and the CD4 percentage, should always be documented, as well
297 as response (virological response and immune recovery) by baseline CD4+ cell strata.

298 **3.2.3. Clinical endpoints**

299 The occurrence of HIV-related clinical events, including AIDS-defining conditions, should always be
300 detailed in clinical study reports. The CDC criteria of 1993, excluding CD4+ T-cell count as an AIDS-
301 defining event, should apply.

302 **3.3. Dose finding studies**

303 **3.3.1. Monotherapy studies**

304 Monotherapy studies in HIV infected patients should be performed in the initial stages of the clinical
305 development programme, after appropriate virological investigations and pharmacokinetic
306 investigations in healthy subjects (see sections 2.1.1. and 2.4.). The purpose is to characterize the
307 relationship between dose, plasma concentration and the short term in-vivo antiretroviral activity of
308 the new agent. The results should form the basis for the selection of doses for further study. Such “de
309 facto” monotherapy studies, where the investigational agent is the only antiretroviral drug
310 administered to HIV-infected patients, should only be performed in treatment naive patients without
311 advanced disease.

312 The duration of monotherapy should take into account the anticipated risk of selecting for resistance to
313 the test agent and should be the minimum needed to meet the objectives of the study, normally 7-10
314 days. Early and repeated determinations of viral load and drug concentrations are recommended.
315 PK/PD modelling may be a useful complementary tool for dose selection. Depending on these
316 considerations, the monotherapy phase might need to be followed immediately by an active
317 combination regimen to minimize the risk for selection of resistant virus when the new agent is
318 stopped.

319 For agents targeting host receptors (e.g. some entry inhibitors) studies in healthy volunteers may also
320 be of use to define the drug exposure necessary for target saturation.

321 **3.3.2. Combination studies in treatment naive patients**

322 Co-administration of the experimental agent when administered in combination with other
323 antiretrovirals should be explored initially in smaller scale studies that characterise the efficacy and
324 safety of one or more dose regimens of the new agent compared to that of a relevant reference
325 product when each is administered in combination with other suitable agents. These studies should
326 follow a sound analysis of the available virological and pharmacokinetic data to support dose regimen
327 selection and should be of randomized double-blind design. The efficacy endpoint used for further
328 decision-making in such studies is usually at 16-24 weeks, although it is recommended that the
329 planned study duration is longer.

330 Patients with more pronounced immunosuppression (e.g., CD4+ cells < 200/μL) or symptomatic
331 patients should be included in phase I/II studies only if there is a specific scientific rationale and if
332 promising efficacy and safety data are already available from patients with higher CD4+ T-cell counts.

333 Combination studies should be performed in such a way that putatively relevant differences between
334 doses in antiviral efficacy and the risk of selecting for resistance can be detected; i.e. the assumption
335 that adding the new agent to the background regimen increases efficacy over and above the
336 background alone should not be doubtful. As an example, dose ranging a new agent in treatment naive
337 patients, in combination with tenofovir and a boosted PI, would likely not render the study capable of
338 showing differences in efficacy between different doses of the new agent, given the usual study sizes.
339 Such designs should be avoided.

340 **3.3.3. Dose finding in patients with viral resistance relevant to the drug** 341 **class to which the new agent belongs.**

342 It may be that virus with resistance to other drugs in the same class as the new agent is likely to be
343 susceptible to the new agent. Such resistant variants may have similar EC50/90 for the new agent as

344 has wild-type virus. It should be noted that in such cases, the barrier to resistance of the new agent
345 might still be impacted by the resistance mutations conferring decreased susceptibility to other agents
346 of the same class.

347 It may also be that EC50/90 is higher than wild-type, but it is expected that the new agent will still
348 exert a clinically relevant antiviral effect provided that adequate drug exposure is achieved. In such a
349 case, it is possible that higher doses or a different dose regimen (e.g. twice daily rather than once daily
350 dosing) might be needed for patients whose virus has reduced susceptibility to the new agent, in order
351 to reach the maximal efficacy.

352 For agents with a potential for use against virus resistant to other drugs of the same class, a
353 satisfactory initial monotherapy study in the treatment-naïve should be followed by a dose finding
354 study in patients infected with these types of viruses. For example, patients failing therapy after at
355 least 8 weeks of stable ART and with documented viral resistance by population sequencing (i.e. in a
356 major viral population) during the screening period could be randomized to one or several doses of the
357 new agent or to placebo, each administered in conjunction with the failing regimen. Such studies
358 should generally have a short term virological endpoint (e.g., after 7-14 days of therapy). Design
359 considerations for such a study are largely similar to those discussed below in **section 3.4.3**.

360 **3.4. Confirmatory studies**

361 **3.4.1. General considerations**

362 Confirmatory studies should aim to document and explore the possible reasons for the variability in
363 efficacy that is observed. To this end it is important that every effort should be made to identify the
364 reasons for virological failure in individual patients.

365 Adherence to therapy is of vital importance for treatment outcome. Major efforts to encourage and
366 document adherence should be made. As a minimum, pill counts and questioning regarding adherence
367 should be performed. Since poor adherence tends to obscure differences in efficacy, it may render the
368 results of non-inferiority trials non-interpretable. Sponsors may define a lower level of adherence
369 required to qualify for a per protocol population.

370 Confirmatory studies should aim to enrol a representative sample of patients. In particular, sponsors
371 should make all efforts to recruit a representative proportion of women, who have historically been
372 under-represented in clinical trials.

373 **3.4.2. Studies in treatment naïve patients**

374 For reasons explained in 3.1, it is anticipated that randomised controlled confirmatory studies will
375 usually be conducted in treatment naïve patients. Patients should fulfil criteria that indicate a need to
376 start antiretroviral therapy, according to recognized clinical treatment guidelines. The existing guidance
377 regarding selection of an appropriate non-inferiority margin should be followed (CPMP/EWP/2158/99).
378 It is recommended that any alternative approaches to study design and/or novel approaches to
379 selection of an appropriate non-inferiority margin should be discussed in advance of study initiation
380 with EU Regulators. Studies should generally be double-blinded. If the sponsor considers that the study
381 cannot be conducted under double-blind conditions, this should be subject to regulatory scientific
382 advice prior to starting the study.

383 The study sample size should be large enough to allow for the conduct of meaningful exploratory
384 subgroup analyses with respect to other factors that potentially affect outcome, such as estimated
385 background regimen activity, viral subtype, sex and ethnicity. Patients should be stratification for the

386 most important prognostic factors and as a minimum by baseline viral load and CD4 count.
387 Furthermore, as differences in antiviral efficacy may be apparent only in patients with a high baseline
388 viral load, studies investigating the initiation of therapy in untreated patients should contain a sizable
389 proportion of patients with a baseline viral load $\geq 100,000$ copies/ml.

390 The study should generally employ randomisation of all patients to receive the new agent or another
391 agent, each given in conjunction with the same other agents. If the sponsor wishes to compare the
392 new agent with a reference agent, each against different backgrounds (e.g., tenofovir/emtricitabine
393 and abacavir/lamivudine, respectively), it is recommended that the sponsor seeks regulatory scientific
394 advice prior to study start; if this approach is considered reasonable, the background regimen should
395 be a stratification factor. The comparator selected should enable a double-blind design, and should not
396 cause inadvertent "unblinding", e.g., due to a characteristic adverse event profile.

397 The proportion of patients with virological suppression at 48 weeks is the appropriate primary
398 endpoint. The total study duration is recommended to be at least two years, to provide long term
399 safety and efficacy data. Important secondary efficacy endpoints include the proportion of patients
400 counted as experiencing treatment failure due to lack of virological efficacy or virological failure, the
401 proportion of patients with detectable or quantifiable viraemia below the defined cut-off for virological
402 failure (if different from the assay LLOQ), as well as the proportion of patients with HIV that develops
403 resistance to one or more antiretroviral agents.

404 **3.4.3. Studies that include patients with viral resistance relevant to the** 405 **drug class to which the new agent belongs**

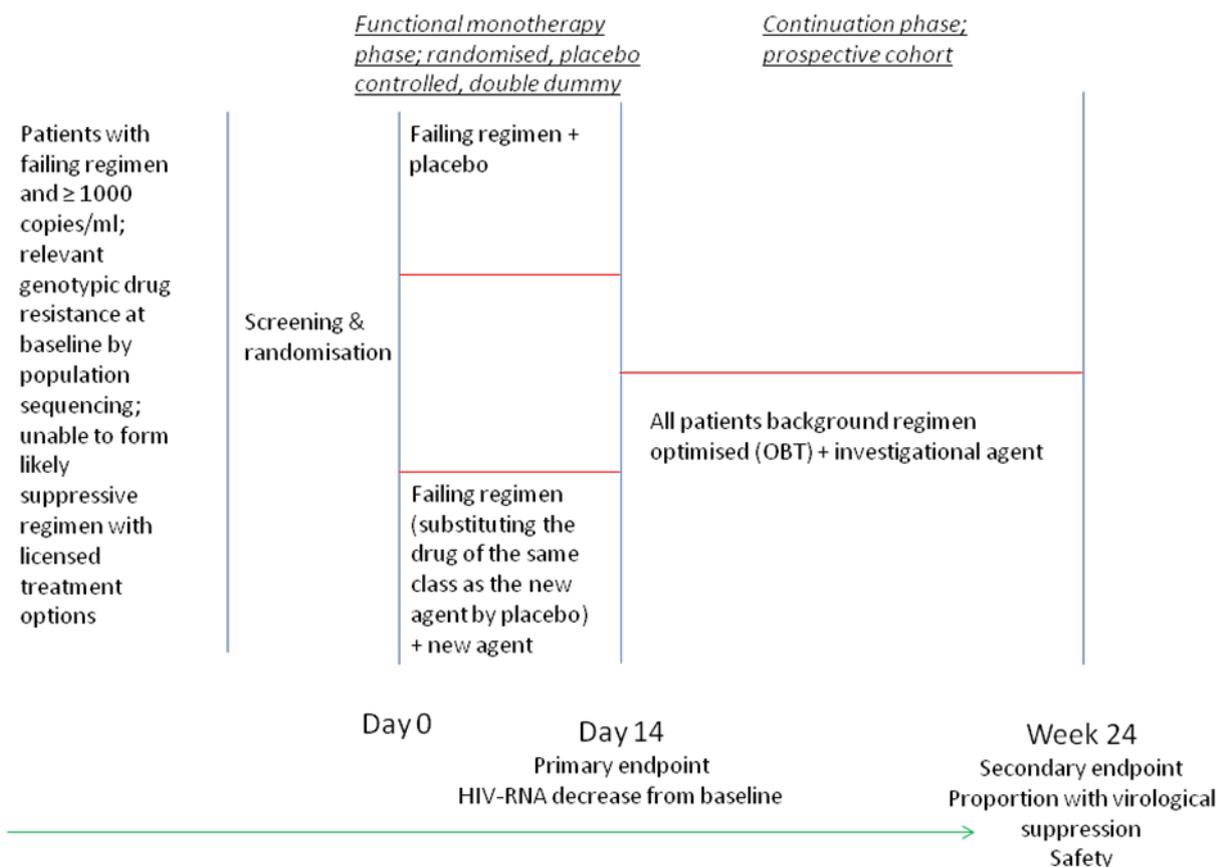
406 Clinical studies to evaluate the efficacy of a new agent of an existing class against viruses that show
407 resistance against at least one agent in the same class (i.e. referred to as class resistance below)
408 should follow on from a sound documentation of in-vitro activity and studies as described in section
409 3.3.

410 The first prerequisite for inclusion of a patient in a study as described below, is viral resistance relevant
411 to other agents of the same class as the new agent in the major virus population (i.e. detectable by
412 population sequencing at screening). The reason for this is that the primary efficacy variable follows
413 short term "functional monotherapy", as outlined, and it is assumed that much of the detectable effect
414 will be exerted on the dominant viral population. What constitutes resistance relevant to other drugs in
415 the class needs to be justified on a case to case basis.

416 A second prerequisite is that such studies be conducted in patients that are in need of the new agent in
417 order to create a likely suppressive regimen. The baseline viral load of patients should be at least 1000
418 copies/mL, to allow for population sequencing, and to ensure a reasonable dynamic range (down to the
419 limit of quantitation of the method used for measurement of plasma HIV-RNA), to ascertain assay
420 sensitivity of the trial. Sufficient representation of differing OBT activities and different levels of
421 resistance to the test agent should be captured.

422 Patients to be included should be on a failing regimen that was unchanged for a minimum of 8 weeks.
423 The failing regimen should include a relevant agent from the class that the new agent belongs to, and
424 the study should be a double blind,, double dummy trial, as outlined below. Resistance to drugs in the
425 class, of relevance for the intended use of the new agent, should be demonstrated by population
426 sequencing at screening. If the latter is not feasible at all study sites for logistical reasons, prior
427 documented resistance could be accepted as inclusion criteria. However, sampling for resistance would
428 always have to be performed at baseline, and only those with relevant drug resistant variants present
429 at this time point by population sequencing should be part of the primary efficacy analysis.

430 To assess efficacy without putting patients with limited remaining options at risk, the following study
 431 design is suggested:
 432



433
 434
 435

436 **A) Short term “functional monotherapy” (e.g. maximum 14 days)**

437 In the following, the term “functional monotherapy” refers to the addition of a new agent to a failing
 438 regimen, without any change in the latter other than the withdrawal of an agent of the same class, for
 439 which the new agent is substituted. In accordance with common usage, it does not in a strict sense
 440 imply that the failing regimen entirely lacks residual antiviral activity. Moreover, it is acknowledged
 441 that a clinically relevant selection pressure favouring less fit, resistant variants, may be exerted by the
 442 continued use of agents in the failing regimen.

443 During this first study period patients are randomized to substitute the new agent for the old agent in
 444 class, or to continue with the latter, while otherwise not changing the failing regimen. This design
 445 would apply to drugs of the same class as an agent in the failing regimen, presumably competing for
 446 the same site of action. An exception to this are NRTIs, for which such a substitution would be relevant
 447 for drugs that are analogues of the same base as an agent in the failing regimen, or which, according
 448 to available clinical and in vitro data, select for the same resistance mutations indicating that co-
 449 treatment might not be rational.

450 The duration of this period of functional monotherapy could vary. The maximal allowable duration of
 451 this phase will be dictated by the known properties of the drug and risk of acquiring resistance with
 452 very short term exposure. In most cases 7-14 days is the recommended duration for the comparative
 453 short term monotherapy phase of the study. Given the very limited duration of this double blind phase
 454 the relatively high pill count caused by the double dummy design is not expected to impact adherence.

455 A staggered design, where patients initially randomised to placebo/reference substance + failing
456 regimen for, e.g., two weeks, are subsequently treated with the test agent for a similar period of time
457 prior to optimizing the background, should be considered. In this case, exposure to the test agent
458 would be similar, provided that the time of the secondary (24 week) endpoint differed by two weeks
459 between arms, in relation to study start.

460 The number of patients should be large enough, and the degree of resistance sufficiently variable, to
461 certify that a comprehensive assessment of the activity by baseline resistance can be achieved. If
462 supported by results previously obtained in vitro and in clinical studies, at least two doses of the new
463 agent should be considered, provided that this can be justified on the basis of available pre-clinical and
464 clinical safety data. This applies both for this period of functional monotherapy and for the study period
465 that follows.

466 If two doses are compared, consideration should be given to:

467 - Primary stratification by baseline resistance (relevant to the class) defined by resistance
468 pathways (based on the available understanding of the evolution of resistance to drugs in the
469 relevant class) or by other relevant categories (e.g. expected lower-level, higher-level resistance
470 to the new agent) as appropriate in the given case

471 - Secondary stratification by the predicted activity of a subsequent OBT

472 The primary end point of this period is the viral load reduction from baseline to end of monotherapy
473 with the new agent, compared to that seen with placebo. A pre-specified level of viral decline
474 considered clinically relevant should be justified by the sponsor, and should take into account the
475 remaining activity of the drug in proportion to that seen in monotherapy studies in patients with wild-
476 type virus. This phase of the study will likely be very similar in design to a phase II study in a similar
477 population (see section 3.3.3); by virtue of being larger, however, it allows for the investigation of
478 activity in a broader population, perhaps with a more diverse population in terms of viral resistance
479 patterns; also, short term monotherapy response can be correlated to longer term effect in the
480 continuation phase, within a more diverse population in terms of viral resistance as well as background
481 regimen activity.

482 B) **Continuation phase; safety and durability of response**

483 After the first phase described above, all patients should get treatment with the new agent (if
484 appropriate more than one dose) in conjunction with an individually optimised background regimen
485 (i.e. in place of the prior failing regimen). The efficacy objective of this phase is to study response
486 rates at 24 weeks (secondary efficacy endpoint) and on through 48 weeks, by degree of baseline
487 resistance and activity of OBT. Furthermore, this phase is of importance for the safety assessment, and
488 particularly so if a higher dose is used in this population, compared to the treatment naïve studies (see
489 section 4). In such cases, at least 48 weeks of follow-up is mandated.

490 These analyses are non-primary end points, to be used to further understand the durability of the
491 antiviral effect, and the need for support from co-treating agents. The longer term outcome achieved
492 with test agent and OBT should be assessed and presented according to genotypic, and if appropriate
493 phenotypic, sensitivity scores predicted, counted from start of optimized therapy. This analysis plan,
494 including definitions for the sensitivity score, should be prospective, but the applicant should also
495 submit the dataset to retrospective explorative analysis, in order to provide a maximal understanding
496 of the parameters that are predictive of success, including the need for support from the background
497 regimen of the new agent.

498 **3.5. Fixed dose combination medicinal products**

500 The specific guidelines for the development of FDC should be consulted (CPMP/EWP/240/95). If the
501 FDC is to be used in the place of a well-documented combination of two or three individual single-drug
502 formulations, the application may be based primarily on demonstrating bioequivalence between the
503 FDC and the free combination of anti-retroviral agents in the fasting and/or fed state in accordance
with the dosing conditions for individual agents.

504 In cases where a new posology is foreseen for the FDC it is recommended that the programme is
505 discussed with EU Regulators to identify the degree to which the application may be supported by
506 PK/PD data. If the FDC includes a new anti-retroviral agent and/or a new pharmacokinetic enhancer
507 then a full clinical development programme will be required.

508 For FDCs intended for use in children, special considerations are warranted as regards age/weight
509 related differences in clearance or bioavailability of the individual components of the combination and
510 the need for sufficient dose forms to accommodate dose adjustment by weight.

511 **3.6. Studies in special patient populations**

512 **3.6.1. Studies in children**

513 The development of acceptable and palatable pharmaceutical formulations with suitable strengths for
514 children is normally expected to take place early in drug development. In case FDC are developed for
515 use in the paediatric population, it is expected that acceptability and palatability of these formulations
516 is an integral part of the development. Dose selection is generally based on results from
517 pharmacokinetic studies, where doses for different age groups are selected to produce plasma levels
518 similar to those observed in adults. Relevant CHMP guidelines should be taken into account (Role of
519 Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population
520 CHMP/EWP/147013/04; Reporting the Results of Population Pharmacokinetic Analyses
521 CHMP/EWP/185990/06; Clinical investigation of medicinal products in the paediatric population –
522 CPMP/ICH/2711/99 (ICH11)).

523 Under certain circumstances, early dose studies could be performed in children with ongoing therapy
524 and suppressed viral loads, by adding the new agent to the ongoing regimen. This approach could
525 minimize the risk for resistance development prior to identifying an appropriate dose. However, this
526 pre-supposes the documented absence of drug-drug interactions between the investigation agents and
527 the agents used for treatment. Further, it is recognised that no PK/PD data are generated with such a
528 study design; however, as stated below, an assumption underlying the recommendations for paediatric
529 studies, is that the PK/PD relation for antiretrovirals is likely to be similar in children and adults, given
530 the same level of viraemia.

531 Bioavailability and drug clearance may differ considerably between age groups and a sufficient number
532 of children ranging from the very young to adolescents should be enrolled in pharmacokinetic studies,
533 to enable adequate dose recommendations. In many cases dose per weight band (e.g. 10 mg for a
534 child between 10 and 20 kg) is an unambiguous way to express dose recommendations. If possible,
535 the use of WHO weight bands should be considered.

536 A specific demonstration of antiviral efficacy in paediatric patients is not required. As it is assumed that
537 the PK/PD relation for a direct acting antiviral is roughly similar regardless of the age of the patient,
538 the efficacy of a dose that yields sufficiently similar exposure in children, compared to adults, would be
539 inferred. The parameters that would be applied to conclude on similarity should be based on available
540 data from the entire development programme, including PK and efficacy data in adults.

541 Therefore non-comparative data in children on the tolerability and safety of the proposed dose
542 regimens as well as documentation of adherence should be generated over appropriate time-spans.

543 Data collected over 24 weeks would form a reasonable basis for the evaluation of a paediatric
544 indication. Large inter-individual variability in pharmacokinetics is common for antiretrovirals, and
545 particularly in children, making population PK an important objective of these studies.

546 The number of treatment naïve children is low in the EU, and mostly limited to the very young. Older
547 children and adolescents are to a great extent suppressed on successful therapies and those failing in
548 many cases do so for reasons of poor adherence, making them less suitable for clinical trials (and
549 particularly where PK evaluation is crucial). Therefore, switch studies in suppressed children, if deemed
550 feasible for the new agent with respect to the drug qualities, is one possible way forward. Such studies
551 are not likely to include the youngest children. Dose suggestions for that group could be based on
552 more limited PK data obtained during add-on to existing regimens, as suggested in first paragraph, in
553 combination with modelling.

554 Long-term post-marketing and pharmaco-epidemiological studies are encouraged.

555 **3.6.2. Studies in older patients**

556 No specific studies are expected in older patients. However, as the lifespan of HIV-infected patients
557 continues to increase it should become increasingly feasible to enrol representative numbers of older
558 subjects in adult clinical trials. During the clinical development programme the potential impact of
559 increasing age on pharmacokinetics should be adequately investigated. For example, drug elimination
560 in light of the age-related decrease in renal function and the potentially higher risk of DDIs since the
561 number and range of co-administered agents is likely to be greater in older subjects.

562 **3.6.3. Studies in pregnant women**

563 For some agents, potentially important changes in PK may occur during pregnancy. Therefore, the
564 pharmacokinetics of new antiretrovirals during pregnancy should be studied if use during pregnancy is
565 anticipated, with particular focus on changes in the second and third trimester. Comparisons both with
566 pharmacokinetics post-pregnancy (same patients), as well as historical non-pregnant controls, are
567 recommended. Due to putative changes in protein binding, the unbound fraction should be assessed
568 whenever relevant and feasible.

569 Concerning the post-marketing monitoring of exposure and safety in pregnancy, see Guideline of the
570 Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation data
571 EMEA/CHMP/3133666/2005.

572 **3.6.4. Studies in patients co-infected with hepatitis B or -C**

573 Patients who are co-infected with HIV and HCV and/or HBV constitute an important, and in some sites,
574 large proportion of HIV-infected individuals. Hence, it is important that such patients are represented
575 in adequate numbers in the pivotal studies, to confirm hepatic safety in patients with chronic hepatitis
576 infections.

577 When the new anti-retroviral agent also shows activity in non-clinical studies against HBV or other
578 viruses that may co-exist in HIV-infected individuals, the potential for a clinically important effect when
579 the agent is used in an ART regimen should be assessed during clinical studies. The risk of selecting for
580 resistance to the new anti-retroviral agent in the co-infecting virus, and the potential for cross-
581 resistance to agents commonly used to treat that virus should be evaluated. However, if nonclinical
582 data suggest that the risk of resistance in one or more potentially co-infecting viruses is very high, the

583 new anti-retroviral agent should probably not be evaluated in such patients.

584 If the applicant intends to develop the new anti-retroviral agent also as a possible treatment for a co-
585 infecting virus, it is essential to determine whether the dose regimen that is to be used for ART may
586 also be effective against the other virus. Since the clinical development may be rather complex the
587 applicant is strongly advised to seek CHMP scientific advice.

588 **3.6.5. Tuberculosis co-infection**

589 Tuberculosis is frequently seen in HIV patients, and is the most common AIDS-defining event in some
590 regions. Before initiating studies, particularly in regions with a high TB prevalence, it is crucial that
591 relevant drug-drug-interactions studies have been performed, to allow for adequate use of TB agents
592 in patients in need of TB therapy during the study.

593 **3.6.6. HIV-2 infection**

594 Patients in need of treatment and infected with HIV-2 presently have few treatment options. If *in vitro*
595 findings indicate that the experimental agent show promising activity against HIV-2, clinical studies in
596 this population are encouraged.

597 **4. Clinical Safety**

598 As for all other medicinal products, the size of the safety database that would be required before initial
599 approval of an antiretroviral agent or before approval of additional indications and alternative dose
600 regimens must always take into account the demonstrated and anticipated benefits and risks.

601 Generally safety data on 500-1000 patients treated for 48 weeks with the relevant dosing regimen
602 have been available at the time of initial approval for use in treatment naïve populations. If a new
603 agent has not been studied in the treatment naïve but appears to have benefit in patients with limited
604 treatment options then a smaller safety database and a shorter duration of exposure may be
605 acceptable, subject to the actual data that are available.

606 As discussed in section 3.3, it is possible that higher doses and/or a different dose regimen might be
607 needed to maximally suppress virus that has reduced susceptibility to the new agent, compared to wild
608 type virus. Such alternative regimens may have a different safety profile compared to regimens
609 investigated for the treatment of patients with fully susceptible virus, but the number of patients that
610 need to receive an alternative regimen in pre-licensure studies may be limited. In these situations
611 there is a need to consider whether the potential safety issues associated with the alternative, higher
612 dose-intensity regimen are of sufficient concern that sound data are required pre-licensure or whether
613 data could be collected during a targeted post-licensure PASS. It is recommended that sponsors
614 discuss with EU regulators on the extent of pre-licensure safety data are deemed to be necessary and
615 how to generate the information.

616 In addition to the usual reporting of safety data during pre-licensure clinical trials the collection of
617 longer-term safety data may be mandated (e.g. beyond the 48-96 weeks duration of studies) in post-
618 marketing studies. These studies should especially focus on safety issues identified as being relevant to
619 the new agent (e.g. based on class-experience, mechanistic reasoning and/or clinical findings).

620 **5. Information in the Summary of the Product Characteristics**

621 For the SmPC section 4.1. (therapeutic indication), a study program comprising studies only in
622 treatment naïve patients could support an indication as follows:

623 *(Product name) is indicated, in combination with other antiretroviral medicinal products, for the*
624 *treatment of adults infected with HIV-1 without present or past evidence of viral resistance to agents*
625 *of the X class (see section 5.1.).*

626 The X class is the class to which the new agent belongs.

627 If a study in treatment experienced patients has also been performed in accordance with the outline
628 above, a wider indication could be supported:

629 *(Product name) is indicated, in combination with other antiretroviral medicinal products, for the*
630 *treatment of HIV-1 infected adults (see section 5.1.).*

631 Sections 4.5 and 5.1 of the SPC are of particular importance for antiretrovirals, since these drugs are
632 often very prone to interactions, and must be used in accordance to predicted drug susceptibility
633 (resistance algorithms) in patients with resistance relevant to the class. Section 5.1. (and if relevant
634 section 4.4.) should also include information pertaining to the likely need for support from co-treating
635 agents, to guide the use of the drug in patients with drug resistance relevant to the new agent or to
636 other antiretrovirals. This must be inferred from available evidence, including, e.g., treatment outcome
637 data and data on the emergence of resistance in case of virological failure. Resistance data should be
638 up-dated when appropriate, based on the emergence of new information.

639 **6. References**

640 1) European recommendations for the clinical use of HIV drug resistance testing: 2011 update, *AIDS*
641 *rev 2011*

642 2) A Meta-analysis to Assess the FDA DAVP's TLOVR Algorithm in HIV Submissions Smith et al, *Drug*
643 *Information Journal 2011*