Novel clinical trial designs for the development of new antiretroviral agents

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The resounding success of combination antiretroviral efficacy for both treatment-naïve and -experienced patients – with 70% - 90% viral suppression rates in recent studies– has made registration trials for new agents challenging. With the inevitable specter of drug resistance, new agents must have a pathway to approval. The Forum for Collaborative HIV Research obtained input from concerned stakeholders including industry, clinical sciences, community advocacy and regulatory sciences (Food and Drug Administration and European Medicines Agency) to discuss how safety and efficacy of new agents could be demonstrated. Recognizing the shortfalls of superiority or non-inferiority trials in this environment, a new trial design for treatment-experienced patients, minimizing the risk for drug resistance but allowing full assessment of safety was proposed. The antiviral efficacy of an active investigational drug would be assessed by comparison to placebo as an add-on to a failing regimen in a short, 10–14 day study followed by institution of an optimized background regimen in both arms with investigational drug given to all patients. The follow-on stage would assess dose response, safety, durability of initial response and development of resistance. Additionally, a second safety trial could be conducted comparing patients randomized to the investigational agent plus a new OBR to those on a new OBR plus placebo. Finally, approval decisions could consider other long-term safety endpoints. Exposing treatment-naïve patients to investigational agents remains a controversial issue; stakeholders have different interpretations of risk-benefit for trials in this population which necessitate careful consideration before initiating trials in them.

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Background

The success of HIV drug development, yielding 26 unique antiretroviral (ARV) drugs (plus alternative formulations and fixed-dose combinations) from six different therapeutic classes allows the construction of safe, effective, tolerable and durable regimens, often individualized by using drug resistance testing, for the

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majority of patients with access to treatment. This unparalleled success presents considerable challenges for future drug development.

For trials of treatment-experienced patients, optimized background regimens (OBR)[1] have become so effective that demonstrating statistical and clinically meaningful improvement from addition of a new ARV to OBR is difficult. For clinical trials of treatment-naïve patients, highly potent, generally well-tolerated, and convenient with once-daily dosing first-line regimens, raise a challenge to demonstrate further improvements. Thus, superiority trials, a trial approach that historically has led to rapid approval of HIV drugs, have become increasingly unlikely to succeed in either patient population.

The feasibility of a common alternative to a superiority trial, the non-inferiority (NI) trial, is limited for treatment-experienced populations by the complexities in determining an appropriate NI margin. Other challenges include differing reasons for regimen failure between treatment arms (e.g. efficacy versus toxicity), difficulty in finding the right patients, and recruitment barriers when certain drugs are restricted in the OBR.

The Forum for Collaborative HIV Research (Forum) invited experts to provide insight regarding challenges in designing clinical trials for treatment-experienced and treatment-naïve patients, and to propose potential new clinical trial designs. Expert contributions were made by representatives from the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), academia, patient advocates, and industry. This paper is the fourth in a series of publications addressing issues in clinical research policy and practice sponsored by the Forum at key points in the history of HIV drug development [1–3]. Like the previous publications, this manuscript is based on deliberations and reflections of the experts, provides a review of the current thinking within the field, and is not intended to represent official guidance.

Treatment-experienced populations

Current trial design barriers

Superiority trials (a new drug plus OBR is compared to OBR plus placebo) have been the usual trial design for a treatment-experienced indication, but are now facing inherent disadvantages. For instance, patients who cannot construct a fully suppressive regimen without a new drug, if randomized to placebo for a prolonged period, risk development of resistance to their remaining available drugs, jeopardizing their future chance for a suppressive regimen. Furthermore, an OBR success rate of 70% or higher (depending on baseline drug susceptibility) [4–8], challenges the demonstration of superiority of an investigational new drug. Also, recruitment of patients with few available treatment options in developed countries is difficult due to the aforementioned advances in therapy.

The results of two pivotal Phase 3 vicriviroc efficacy trials, VICTOR-E3 and 4 illustrate these concerns [9]. These identically-designed, 48-week randomized Phase 3 trials enrolled patients with documented resistance to two or more available drug classes or ARV experience of at least six months with HIV RNA >1000 copies/ml [9]. Viral suppression (<400 copies per mL) occurred in 72% of patients randomized to vicriviroc plus OBR versus 71% in patients randomized to placebo plus OBR (p=0.6). Overall superiority of vicriviroc compared to placebo, therefore, could not be demonstrated. However, in a retrospective subset analysis, patients in the active arm, with baseline phenotypic sensitivity score of 2 or less (two or fewer fully active drugs) had a 70% virologic success rate compared to 55% in the control arm. These results suggest that superiority cannot readily be demonstrated in clinical trials involving patients with two or more fully active drugs available to build the OBR.

The prevalence of patients with multi-drug resistant virus has decreased substantially in developed countries, in part due to increasing use of boosted protease inhibitors (PIs) and the overall enhanced potency of ARV regimens,[10] thus making recruitment of such patients a challenge. For example, from 2006 to the present, the rate of patient recruitment for trials of treatment-experienced patients with multiple drug resistance has fallen from 1.15 per month to 0.02 per month (Table 1). This dramatic reduction in recruitment rate has occurred despite sponsors broadening the entry criteria related to resistance levels (Table 1, column 1), and using an ever-increasing number of study sites and countries. For example, the SAILING trial (ING111762, Table 1), investigating the efficacy of dolutegravir, an integrase inhibitor, in treatment-experienced patients with resistance to at least two ARV classes, was initiated in October 2010 and is still recruiting. Investigators anticipate that recruitment rates will be as low or even lower than those for the elvitegravir trials [11].

While NI trials have been considered an alternative design for treatment-experienced patients, establishing the NI margin is not straightforward. The FDA's approach to establishing an NI margin has been to look at the benefit of a comparator drug over placebo while trying to preserve at least 50% of the active control's effects [12]. For example, if the treatment difference and 95% confidence interval (CI) between two past regimens was 32% (22, 42), a 11% margin (or half the lower bound of the 95% CI) could be justified. The NI margin justification should address the effect size of the control drug in the setting of the planned trial, requiring an assumption of the constancy of that effect. Ensuring assay

Table 1. Rate of patient recruitment for recent HIV trials.

Clinical Trial	Number of Subjects	Number of Countries	Number of Sites	Recruitment Period	Recruitment Rate/Patient/Site/Month
BENCHMRK-1 (3-class resistant) [8]	350	12	61	~ 5 months (2006)	1.15
VICTOR E-3, E-4 [9] (2-class resistant or ≥6 month treatment experienced)	857	North America, Europe, Latin America, South Africa	160+	~ 12 months (2007/2008)	0.45
Elvitegravir (any resistance or ≥ 6 month experience of 2 classes) [33]	700	14	183	~ 14 months (2008/2009)	0.27
Lersivirine Phase 2 (NNRTI resistance; pre-protocol amendment) [34]	189	11	55	~ 8 months pre-amendment (2009/2010)	0.02
ING111762 (2-class resistance) (currently recruiting)	688	20	226+	Ongoing	Ongoing

Table courtesy of Sara Hughes and adapted from the ''Emerging issues in clinical trials for new ARV development'' meeting available at http://www.hivforum.org/storage/hivforum/documents/2010ClinicalTrials/2_3_hughes_572_experience_final[1].pdf.

sensitivity of an NI trial and its margin depends on the ability to apply historical data and conditions to the current trial as closely as possible. This may not be straightforward given the success of newer agents and improvements in response rates over time. The availability of several new potent drugs with which to construct individualized OBRs means the comparator arm is increasingly likely to be more effective than a historical comparator regimen, even given the same estimated genotypic/phenotypic sensitivity score [9]. Ascertaining adequacy of the constancy assumption may be difficult due to historical trial differences in baseline patient characteristics (drug susceptibility, baseline viral load, and CD4 cell counts); use of newly approved background drugs; and variation in response rates for newer therapies.

The sample size dependency on the NI margin presents another challenge; it is usually larger than for superiority trials. The width of the NI margin drives the overall sample size (Fig. 1); a decrease in NI margin from 15% (lower 3 lines) to 10% (upper 3 lines), doubles the required sample size. In short, the sample sizes for NI trials may be even larger than the already considered large sized superiority trials.

New perspectives for phase 3 clinical trials

Dissociating efficacy and safety evaluations

Superiority trials offer the most direct demonstration of efficacy since they avoid reliance on previous trials to estimate the efficacy of the investigational agent in relation to standard-of-care, but superior efficacy has become difficult to demonstrate in traditional terms (described above). A short duration, step-wise superiority design alternative, allowing a clear assessment of the antiviral potency of an investigational drug within a short enough time frame to prevent the development of drug resistance, was proposed.

Figure 2 illustrates a short step-wise superiority trial design. Patients experiencing virological failure on their current regimen, who would need a new, active drug to construct a viable regimen, continue their failing regimen and are randomized to placebo or a new investigational drug. Randomization to the investigational drug could proceed at one or more doses. The primary efficacy evaluation of the investigational new drug compared to placebo occurs after 10-days to 2 weeks, depending on individual drug characteristics, before the risk of resistance development to the new drug, or additional resistance to the background drugs is likely to become significant. After the placebo comparison period, all participants receive the investigational new drug (at a single or different doses) added to a re-optimized background. A second assessment occurs at 24 weeks to evaluate dose response, durability of initial response, safety, and emergence of resistance to the investigational new drug and other drugs in the regimen. However, primary efficacy analysis for the new drug is the short duration viral load comparison to placebo. This may be justified based on: 1) previously shown correlations between mean reduction in viral load (over 16–24 weeks) and reduction in the risk of disease progression [13] and, 2) drugs with low barriers to resistance as monotherapy can still produce long-term activity when used as part of a fully active regimen, as described below.

A smaller, proof-of-concept version of this trial design could be conducted to explore dose response and activity in a highly treatment-experienced population before initiation of confirmatory trials. In the trial design outlined in Fig. 2, a dose response in the full population might not be observed at 24 weeks because doses selected for further study in HIV trials are typically in the plateau range of a dose response curve, at least in patients with little or no resistance to the class. However, patients with multiple drug resistance may have decreased susceptibility to a new investigational drug in an existing class and may require higher exposures for an optimal effect; therefore, evaluating dose response and relationship of response by background susceptibility would be an important assessment that can offer supportive evidence of efficacy. Clearly, patients in whom a new investigational agent is not expected to demonstrate any antiviral activity due to

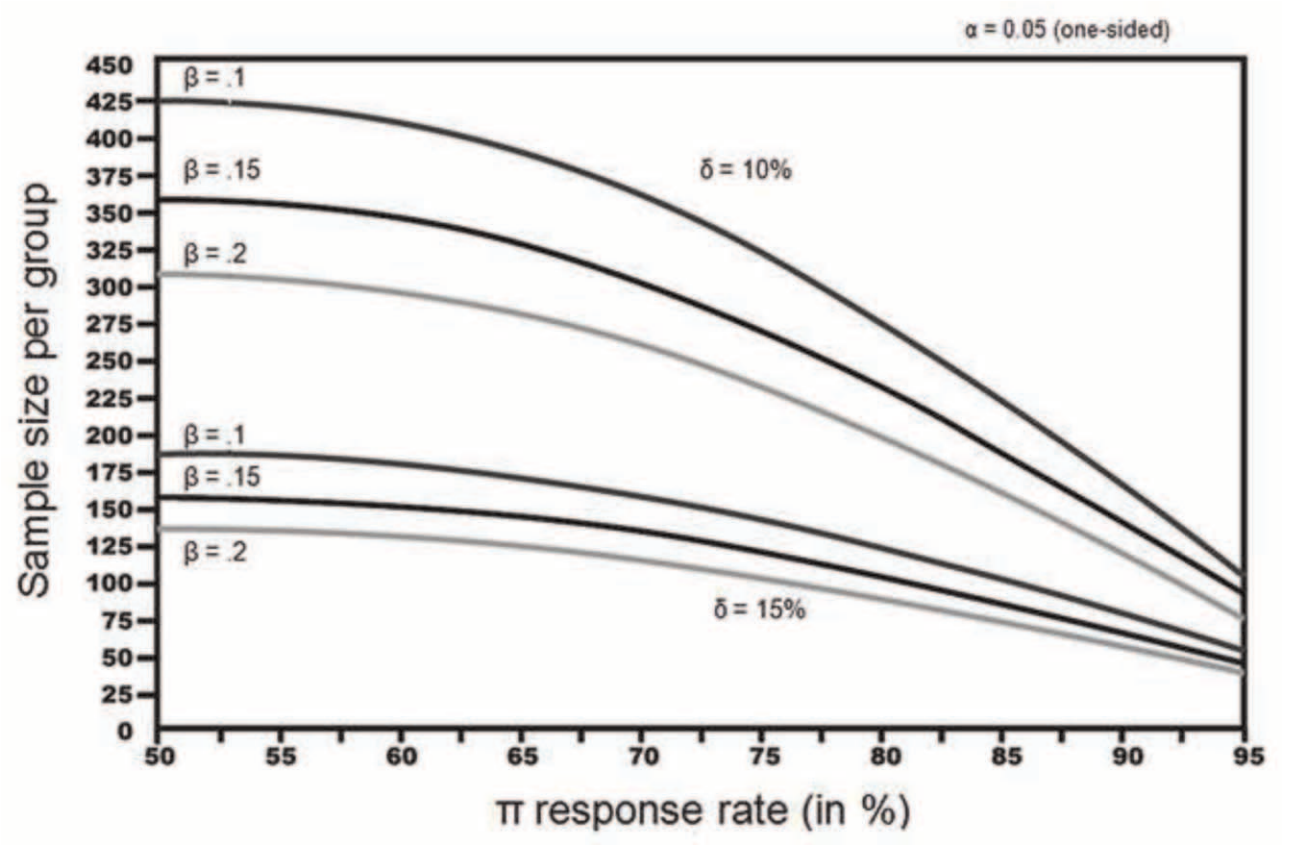

Fig. 1. Schematic representation of the relationship between power, sample size and response rates. Figure courtesy of Victor De Gruttola and adapted from the ''Emerging issues in clinical trials for new ARV development'' meeting available at http://www.hivforum.org/storage/hivforum/documents/2010ClinicalTrials/1_1_degruttola_ni%20trials.forum.pdf.

high levels of cross-resistance should not be considered for such trials.

Treatment-related adverse events occurring at a frequency approximating 1% could be identified from a safety database of 200–300 patients followed for 24 weeks. Enrolling this number of patients means that the trial would likely be statistically overpowered for the primary efficacy endpoint (at 10–14 days of therapy). Over-powering may allow investigation of the impact of different levels of drug resistance in the OBR on virologic outcome. If appropriate, this safety database could be supported by active-controlled trials in treatment-naïve patients. Alternatively, the trial could be powered to rule out potential differences in response between doses at 24 weeks.

Given the potential benefits of a new active drug for HIV treatment in heavily treatment-experienced patients and the difficulties of comparative trials in this group, consideration of the earliest possible endpoint for evaluating a drug's efficacy is justifiable. Note that durability of viral suppression is a function of an entire drug regimen rather than of an individual drug. Drugs with relatively low barriers to resistance and limited durability of virologic suppression when used as monotherapy have nonetheless demonstrated potent and durable effects when used as part of appropriately suppressive regimens. For instance, ritonavir-boosted PIs have demonstrated prolonged viral suppression as single agents, whereas efavirenz or raltegravir have limited durability of suppression as monotherapy. Yet, efavirenz- or raltegravir-containing regimens have demonstrated treatment responses comparable to ritonavir-boosted PI-based regimen at 48 weeks [14–16]. Therefore, the contribution of an individual agent may be assessed by short-term potency evaluations, whereas longer-term durability may depend on a drug's contribution within the context of a complete regimen. A disadvantage of the proposed, short, efficacy trial is that it might not deliver sufficient understanding of the level of support from other drugs in a regimen that a new agent might require, for example, in terms of its contribution towards barrier to resistance. Other trials would be needed to address this concern.

Some experts proposed an alternative approach. Restating the concept of dissociating evaluations of efficacy from safety, their proposal pairs short-term virologic efficacy evaluations in patients with one or less active

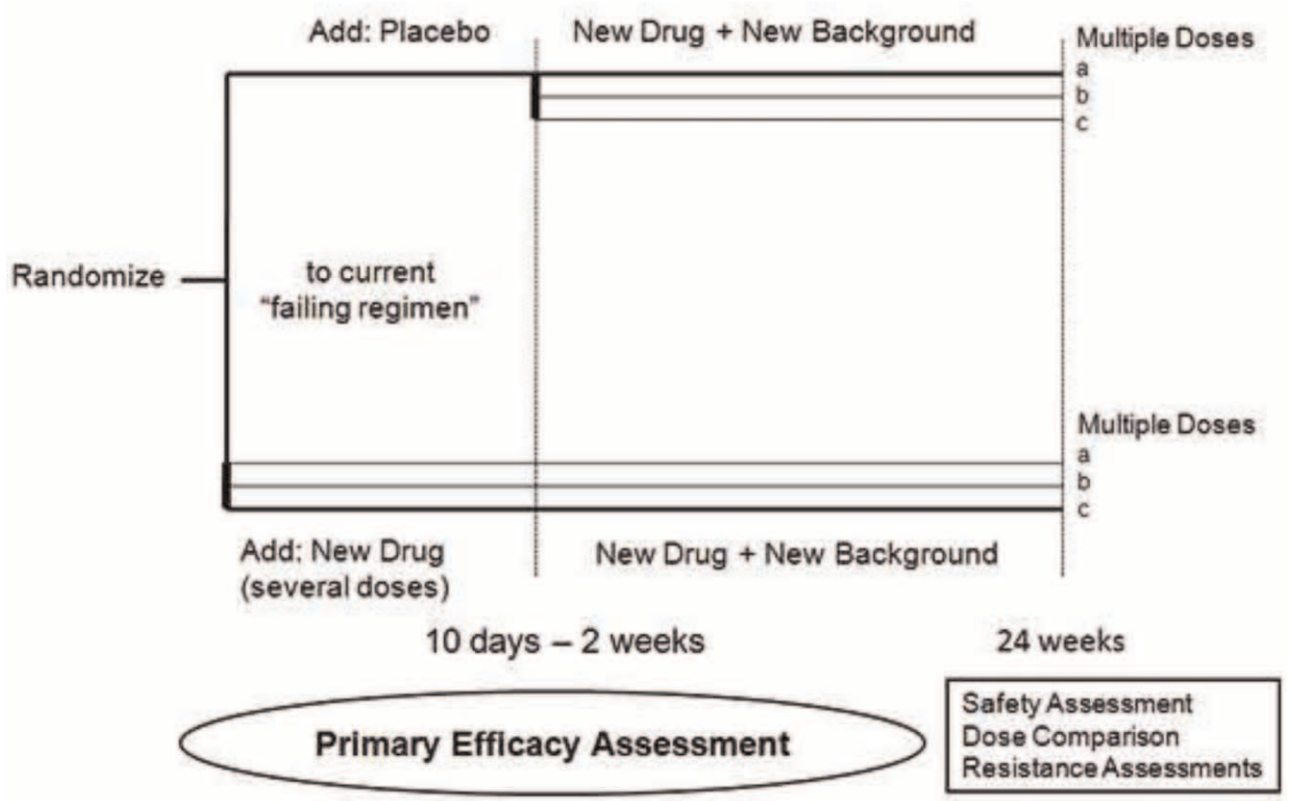

Fig. 2. New HIV trial design pathway for treatment-experienced patients.

drugs available, with a separate longer (24–48 weeks) randomized trial in patients with at least two active drugs available. The major endpoint for the longer trial would be safety rather than virologic response, although virologic or dose response could be an included endpoint. This design would allow the assessment of *comparative* safety while simultaneously shielding subjects from an insufficiently suppressive regimen. Although evaluation of the investigational drug's efficacy would not be the primary consideration, antiviral activity assessments could be derived and used to support efficacy considerations, such as contribution of the investigational agent to the durability of effect, presence of dose-response effect, and response rates among subgroups (e.g. those with viral load levels >100 000 copies/ml). Such trials may be difficult to conduct, as patients would be exposed to a new drug with an unknown safety profile, which per trial design may not provide significant additional efficacy.

A combination of these two trial designs would yield randomization-based comparative safety data, comparative short-term efficacy data, as well as information on durability of efficacy, albeit in a non-randomized manner.

Additional endpoints for consideration

As patients with long-term virologic suppression live longer, co-morbidities such as non-AIDS cancers, and cardiovascular, neurologic, liver and renal disease, have emerged. ARV's may contribute to some of these endpoints [17–20]. Some participants recommended that all trials, whether pivotal or supportive, collect endpoints relevant to cardiovascular and metabolic disease and evaluate organ function. The usefulness of these in differentiating different drugs needs to be established.

Treatment-naïve populations

Current trial design barriers

Viral suppression rates of current first line ARV regimens (highly potent, durable, convenient and generally well-tolerated), exceed 90% in treatment-naïve patients making 48 week superiority studies impractical (Table 2). NI-design Phase 3 trials are a widely accepted alternative, and even when an NI margin is well established, particularly when efavirenz is the comparator, trial outcomes can be challenging to interpret. Although response rates may appear similar, true differences between regimens with respect to safety and virologic failure may exist because the current primary endpoint evaluation is a composite of both safety and virologic changes. Recent trials illustrate this issue.

The ACTG 5142 trial compared 3 first-line regimens: (1) two NRTIs + efavirenz; (2) two NRTI + lopinavir/ritonavir; and (3) efavirenz + lopinavir/ritonavir [21]. At

Table 2. Recent studies of antiretrovirals in treatment-naïve patients*.

Study (reference)	Year of publication	Study Regimen	N	HIV RNA <50 copies/ml at 96 weeks
ACTG 5142 [21]	2008	2 NRTI + EFV	250	89%
		2 NRTI + LPV/r	253	77%
		EFV + LPV/r	250	83%
ARTEMIS [35]	2009	TDF/FTC + DRV/r	343	79%
		TDF/FTC + LPV/r	346	71%
STARTMRK [15]	2010	TDF/FTC + RAL	281	81%
		TDF/FTC + EFV	282	79%
CASTLE [30]	2010	TDF/FTC + ATV/r	440	74%
		TDF/FTC + LPV/r	443	68%
ACTG 5202 [14]	2011	TDF/FTC + ATV/r	465	90%
		TDF/FTC + EFV	464	91%
ECHO/THRIVE [16]	2011	TDF/FTC + EFV	682	78%
		TDF/FTC + RPV	686	78%

Abbreviations: /r, ritonavir-boosted; ACTG, AIDS Clinical Trials Group; ATV, atazanavir; DRV, darunavir; EFV, efavirenz; LPV, lopinavir; NRTI, nucleoside reverse transcriptase inhibitor; RAL, raltegravir; RPV, rilpivirine; TDF/FTC, tenofovir/emtricitabine.
*Studies enrolled different patient populations with different baseline HIV RNA and CD4 cell counts and were conducted and analyzed using different methods; cross-study comparisons are not valid.

week 96, the proportion of patients with plasma HIV-1 RNA less than 50 copies/mL was 89% in the efavirenz arm, 77% in the lopinavir–ritonavir group, and 83% in the NRTI-sparing group. While regimen (1) was superior to regimen (2), the NRTI-sparing regimen (3) was not statistically different from either of the two NRTI-containing regimens. Further complicating the interpretation, both regimens (2) and (3) were shown to be statistically superior to regimen (1) at 96 weeks with respect to increase in CD4 count. At virologic failure more patients developed resistance with regimen (3) than the other regimens. Virological failure with regimen (1) frequently resulted in NNRTI drug resistance whereas regimen (2) led to the least drug resistance following virologic failure. The adverse event profiles seen with the three regimens also differed, with more recovery of limb fat but also higher lipid levels seen in the efavirenz + lopinavir/ritonavir regimen (3); however, no difference in time to trial drug discontinuation due to toxicity was observed between the three regimens. Thus, different regimens appeared optimal depending on the specific endpoint: virologic suppression, CD4 cell count increase, development of drug resistance following virologic failure, and adverse events.

Another example of the complexity of ARV trial design for treatment-naïve patients is the Phase 3 trials of the investigational NNRTI drug, rilpivirine [22]. The two parallel trials enrolled over 1300 treatment-naïve patients and randomized them to receive 2 NRTIs combined with either rilpivirine or efavirenz. At 48 weeks, 83% of the rilpivirine group compared with 80% of the efavirenz group suppressed HIV-1 RNA levels to less than 50 copies/ml. The trials concluded that rilpivirine was NI to efavirenz. The overall response rates appeared similar, but the rate of virologic failure was higher in the rilpivirine group (13% vs. 9%), while the rate of discontinuation due to adverse events was higher in the efavirenz group (7% vs. 2%). The observed failure rate in the rilpivirine arm led to a higher rate of drug resistance and cross-resistance within the NNRTI class compared to efavirenz. Thus, rilpivirine appeared less potent but better tolerated than efavirenz. Because of the analysis methods used, this led to similar overall rates of viral suppression in the intention-to-treat population.

These results highlight the current issues with treatment-naïve trials. Demonstrating clear superiority proves challenging given the high success rate. Interpretation of clinical trials results is challenging when two distinct factors, efficacy and tolerability, each contribute to the primary endpoint.

The timing of treatment-naïve trials in the overall drug development timeline remains controversial for some experts [3]., given the availability of highly effective and preferred standard-of-care regimens for this population. Recent examples illustrate the problem. For instance, trials of novel nucleoside analogue-sparing regimens (raltegravir plus atazanavir [23] and raltegravir plus darunavir/ritonavir [24]) reported unexpected outcomes potentially indicating suboptimal efficacy. The risk-benefit for enrollment of treatment-naïve patients in NI trials may be considered problematic, as these individuals may be put at risk for development of resistance. Instead, some experts believe treatment-naïve patients, particularly those with advanced disease (e.g., CD4 cell counts <200/uL or AIDS-defining illnesses at baseline), should be offered approved therapies rather than investigational agents. Once safety and efficacy data from treatment-experienced trials are available, trials can be initiated in treatment-naïve patients. This would protect treatment-naïve patients from unknown toxicities or losing future ARV options.

Discussion and conclusions

Despite availability of effective ARV therapy from six distinct therapeutic drug classes, the need for new

therapies for both treatment-experienced and treatment-naïve patients remain. Today, evaluation of new drugs in the setting of effective therapy is a major challenge.

Virologic suppression rates exceeding 70% in studies of treatment-experienced patients make successful superiority trials difficult to conduct, except in patients with multiple drug-resistant virus and less than two active drugs available. With the increasing evolution of new agents and drug classes, however, individuals meeting these criteria are increasingly difficult to find and recruit, at least in developed countries. Also, the ethics of including such patients in comparative trials may be problematic.

NI trials do not necessarily offer a viable alternative for all patient populations. Identification of NI margins is challenging and NI trials require sample sizes that may not readily be recruited.

This situation calls for innovative thinking in new drug development. Such adaptations are more likely to be accepted if they are developed through a consensus process involving all stakeholders. The Forum process [25] provides a mechanism to obtain expert insight, foster dialogue and work towards a consensus.

The new proposal for trials in multi-drug resistant patients with few treatment options represents such a modification. The short (10–14 day) comparison of an investigational new agent versus placebo, with the patient's current failing regimen as background, evaluates short-term efficacy in viral load reduction while attempting to minimize the risk for development of drug resistance. Early viral load reduction has been shown through decades of previous work to predict long-term response [13,12,16,26–32]. Each of the 13 ARVs that received accelerated approval based on a 24 -week viral load endpoint retained sufficient viral suppression at 48 weeks to receive traditional approval.

The proposed step-wise approach is a new concept in HIV drug development. The concept recognizes the need to limit the risk of exposure to functional monotherapy while allowing for long term safety assessment. The short-term efficacy evaluation would be followed by ARV regimen optimization and a second assessment at 24 weeks to assess dose response, safety, durability of initial response and development of resistance. The suggestion by some expert participants to conduct a comparative safety trial in patients with a minimum of two active drugs available, randomized to OBR plus an investigational agent or OBR plus placebo would essentially turn trials like the vicriviroc trials, which failed to meet their primary endpoint [9], into trials of comparative safety. Other long-term safety endpoints, such as those related to inflammation, could be considered in approval decisions once appropriately validated.

Similarly, trials in treatment-naïve patients are difficult given the >90% success rates of active-control therapy. Failure to suppress viral replication due to actual drug failure, rather than drug toxicity or tolerability, may be less than 10% at 48-weeks. Many experts believe that, given this degree of success, enrollment in a trial with an investigational agent is not clinically advisable for treatment-naïve patients. On the other hand, new investigational drugs for HIV might offer these patients the prospect of better tolerability or reduced long-term safety risks than currently available options.

These proposed changes in HIV trial design could offer a clearer pathway for regulatory approval of promising new investigational compounds that could be valuable for HIV-infected patients still in need of novel treatment options, or which may have particular advantages in terms of safety and tolerability. This would preserve innovation in HIV drug development which could become even more challenging in the coming years if feasible regulatory requirements are not adopted. Moreover, the study designs being proposed may be more appealing to clinical investigators and study participants as they could enable access to investigational therapies with less risk of jeopardizing future treatment options.

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Conflicts of interest

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