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The future of long-acting cabotegravir plus rilpivirine therapy: deeds and misconceptions

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ABSTRACT

HIV infection is currently managed as a chronic disease because of improvements in antiretroviral therapy (ART). Switching to a new regimen is a natural event during long-term therapy to avoid problems related to toxicity, adherence, failure, and potential selection of drug resistance. The development of co-formulations of multiple agents in one pill, and novel drug classes and drugs with a high genetic barrier to resistance have been important in this context. The approval of the long-acting, once-monthly or bimonthly injectable combination of the second-generation strand transfer integrase inhibitor (InSTI), cabotegravir (CAB) together with the non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine (RPV) represents the most recent achievement in the search for potent and convenient ART. Several pivotal trials (such as LATTE-2, ATLAS, FLAIR, and ATLAS-2M) showed the high efficacy and safety of this long-acting formulation used as an induction-maintenance strategy. Few confirmed virological failures (CVF) have been observed. The combination of at least two of the following baseline factors, HIV-1 subtype A6/A1, a body mass index (BMI) $\geq$30 kg/m^2, and RPV resistance-associated mutations, was associated with an increased risk of CVF at week 48. The data indicate that this long-acting therapeutic strategy is attractive and potent; therefore, defining the most appropriate patient for this treatment and how to handle practical issues is warranted.

1. Introduction

Summer 1996 marked the advent of highly active combination antiretroviral therapy (HAART or simply ART) at the 11th International AIDS Conference in Vancouver, BC, Canada, when the results of the first ART studies assessing combination therapy using two nucleoside analogue reverse transcriptase inhibitors (NRTI) + one protease inhibitor (PI) were brought to global attention [1]. Since then, HIV infection has become a manageable chronic disease, rather than a death sentence. However, subsequent studies showed that life-saving ART regimens were marred by significant toxicity, difficult adherence and, eventually, selection of drug resistance. Substantial improvements have been made, particularly in terms of co-formulation of multiple agents in one pill, and the development of novel drug classes and drugs with a high genetic barrier to resistance. The approval of the long-acting, once-monthly or bimonthly injectable combination of the second-generation strand transfer integrase inhibitor (InSTI), cabotegravir (CAB) together with the non-nucleoside reverse transcriptase inhibitor (NNRTI), rilpivirine (RPV) represents the most recent achievement in the search for potent and convenient ART [First long-acting injectable antiretroviral therapy for HIV recommended for approval, EMA website,16th Oct 2020 https://www.ema.europa.eu/en/news/first-long-acting-injectable-antiretroviral-therapy-hiv-recommended-approval].

David Margolis and colleagues [2] conducted the phase II, dose-ranging LATTE trial in which oral CAB was combined with RPV 25 mg as a maintenance strategy for patients with virological suppression after 24 weeks of induction with standard triple therapy. At baseline, participants were randomly assigned to receive one of three doses of CAB (10, 30, or 60 mg) plus abacavir-lamivudine or tenofovir-emtricitabine, or to the comparator efavirenz 600

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Table 1
LATTE and LATTE-2 studies: summary of PDVF and drug resistance in the CAB + RPV arm

Study	CAB dosage[a]	HIV-1 subtype	BL major RAMs NNRTI	BL major RAMs InSTI	Week at PDVF	VL at SVF/CVF (cps/mL)	PDVF timepoint major RAMs NNRTI	PDVF timepoint major RAMs InSTI	Drug sensitivity at PDVF (fold change)[b] RPV	Drug sensitivity at PDVF (fold change)[b] CAB
LATTE	30 mg	B	None	None	36	-/-	None	None	-	-
[2,11,41,42]	10 mg	B	None	None	48	18 886[48]/-	**E138Q**	**Q148R**	1.83	3.08
	10 mg	B	None	None	72	-/-	**K101K/E, E138E/A**	None	4.60	-
	10 mg	B	None	None	108	385/772	None	**V151V/I**	-	1.05
	10 mg	B	None	None	132	836/1727	**K101E, M230M/L**	None	12.00	-
	30 mg	B	None	None	132	908/211	None	None	-	-
	10 mg	B	None	None	180	243/1748	**K101E, E138K**	**E138K, G140A, Q148R**	21.00	116.00
	60 mg	B	None	None	264	656/304	**K101K/E, E138E/K**	**G140S, Q148R**	1.77	9.84
LATTE-2	Q8	-	None	None	4	-/-	None	None	-	-
[2,7]	Q8	-	None	None	48	-/-	**K103N, E138G, K238T**	**Q148R**	3.3	5.1

In the table are reported participants with PDVF and emergent major resistance mutations (highlighted in bold). The RPV major resistance mutations (K101E/P, E138A/G/K/Q/R, V179L, L100I, Y181C/I/V, H221Y, F227C, M230I/L) reported in the IAS-US list [43] are underlined.
In the LATTE study, PDVF was defined as follows: <1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA by Week 4 OR confirmed HIV-1 RNA ≥200 copies/mL at or after Week 16 or after prior suppression to <200 copies/mL.
In the LATTE-2 study, PDVF was defined as follows: <1.0 $\log_{10}$ copies/mL decrease in plasma HIV-1 RNA by Week 4 OR confirmed HIV-1 RNA ≥200 copies/mL after prior suppression to <200 copies/mL OR >0.5 $\log_{10}$ copies/mL increase from nadir HIV-1 RNA value ≥200 copies/mL.
Dash lines indicate that information is not available.
CAB, cabotegravir; cps/mL, copies/mL; InSTI, integrase stand transfer inhibitor; CVF, confirmed virological failure; FC, fold change; LTFU, lost to follow-up; NNRTI, non-nucleoside reverse transcriptase inhibitor; PDVF, protocol-defined virological failure; RAMs, resistance-associated mutations, according to the IAS-USA list 2011 [44]; SVF, suspected virological failure; VL, viral load.
[a] CAB dosage in the LATTE study: 10 mg or 30 mg or 60 mg. CAB dosage in the LATTE-2 study: 30 mg with a 4-week dosing interval (Q4W) or an 8-week dosing interval (Q8W).
[b] Monogram biological cut-offs: RPV=2.0, CAB=2.5.

mg + abacavir-lamivudine or tenofovir-emtricitabine. Participants with a viral load of <50 copies/mL at week 24 in the CAB groups stopped taking companion drugs and continued with maintenance therapy of CAB and RPV. At week 96, there was a significant difference in virological outcome: 137 subjects (76%) receiving dual therapy had a viral load of <50 copies/mL compared with 39 (63%) of those receiving the efavirenz-based triple therapy. The success of the LATTE trial sparked a series of pivotal trials, such as LATTE-2, ATLAS, FLAIR, and ATLAS-2M, which investigated the induction-maintenance strategy with long-acting CAB + RPV [3–11]. These, in turn, ignited the debate on the future of ART with long-acting compounds in the increasing proportion of subjects achieving stable HIV suppression. The evidence regarding the use of long-acting CAB + RPV is not yet set in stone, thus the purpose of this manuscript is to shed more light on this matter by answering a series of open questions.

2. Does the barrier to resistance differ between oral and long-acting formulations?

Results obtained over 6 years of treatment in the LATTE study support the long-term safety and efficacy of oral CAB + RPV dosing [12]. Few protocol-defined virological failures (8/160) were reported in participants treated with oral CAB + RPV over this period: two were reported through week 48 (one with emergent resistance mutations for both NNRTI and InSTI), one through 48-96 weeks (with NNRTI emergent resistance mutations), three through 96-144 weeks (with one of them with NNRTI-emergent resistance mutations), and two through 144-312 weeks (both presenting emergent resistance mutations for both NNRTI and InSTI) (Table 1). The majority (5/8) of failures occurred in the 10-mg dosing arm, particularly all the five with emergent resistance mutations, whereas only two failures, with no emergent mutations, occurred with CAB 30 mg, which was the final dosage selected for the oral combination.

The efficacy of a long-acting formulation of CAB + RPV has been shown in the phase IIb LATTE-2 study and in the phase III ATLAS, FLAIR and ATLAS-2M studies [3–11].

In the LATTE-2 study, only 2/230 participants experienced virological failure through week 48 on the Q8W dosing arm, one of whom had treatment-emergent NNRTI (K103N, E138G, K238T) and InSTI (Q148R) resistance [2]. No additional virological failures were observed on any arm during five years (256 weeks) under long-acting CAB + RPV [7].

The ATLAS, FLAIR and ATLAS-2M studies demonstrated the efficacy and safety of long-acting HIV treatment with CAB + RPV dosed Q4W (ATLAS and FLAIR), and Q8W (ATLAS-2M), with a virological failure rate of around 1% (n=17/1636) through week 48 across all studies [4, 5, 8]. In a pooled analysis of 591 individuals treated with long-acting CAB + RPV from ATLAS and FLAIR at 48 weeks, emergent NNRTI and InSTI resistance mutations were detected in four of the six individuals experiencing virological failure (one in the ATLAS study and three in the FLAIR study) (Table 2) [6]. The two other failing participants harbored NNRTI resistance mutations, which were already present in peripheral blood mononuclear cells (PBMCs) at baseline. Only one further virological failure was observed between week 48 and 256 in either of the two studies; specifically, a patient in the FLAIR study failed at week 108, with emergent NNRTI and InSTI resistance. Analysis through 124 weeks showed one additional virological failure at week 108 with emergence of NNRTI and InSTI resistance mutations in the FLAIR study (Table 2) [11]. In the ATLAS 2-M study, 10 virological failures occurred through week 48, eight in the Q8W arm and two in the Q4W arm (Table 3). NNRTI resistance mutations were found in 7/8 participants in the Q8W arm. Only 2/7 of these participants did not show any NNRTI mutation at baseline, whereas NNRTI mutations were already present in PBMCs in the other five participants. In the Q4W arm, one of the two participants with failure developed NNRTI resistance. InSTI resistance was detected in five participants in the Q8W arm; in four of them, InSTI mutations emerged un-

Table 2
ATLAS and FLAIR studies: summary of virological failure and drug resistance in LA CAB + RPV Q4W arm

Study	Sex	HIV-1 subtype	BL major RAMs[a] NNRTI	InSTI	Week at SVF/CVF	VL at SVF/CVF (cps/mL)	SVF timepoint major RAMs NNRTI	InSTI	Drug sensitivity at SVF (fold change)[c] RPV	CAB	DTG
ATLAS	Female	A/A1	E138E/A	None[b]	8	79 166/25 745	E138A	None[b]	2.4	0.8	0.9
[4-6]	Female	AG	V108V/I E138K	None	12	695/258	V108I E138K	None	3.7	1.2	1.0
	Male	A/A1	None	None[b]	20	544/1841	**E138E/K**	**N155H**[b]	6.5	2.7	1.2
FLAIR [6,	Female	A1	None	None[b]	20	373/456	**E138E/A/K/T**	**Q148R**[b]	7.1	5.2	1.0
9-10]	Male	A1	None	None[b]	28	287/299	**K101E**	**G140R**[b]	2.6	6.7	2.2
	Female	A1	None	None[b]	48	488/440	**E138K**	**Q148R**[b]	1.0	9.4	1.1
	Male	A6	None	None[b]	108	887/1112	**V106V/A, V108V/I, E138G, M230L**	**N155H R263K**	27.0	9.0	3.8

In the table are reported participants with confirmed virological failure and emergent major resistance mutations (highlighted in bold). Underlined are reported the RPV major resistance mutations (K101E/P, E138A/G/K/Q/R, V179L, L100I, Y181C/I/V, Y188L, H221Y, F227C, M230I/L) resistance mutations reported in the IAS-US list [44].
BL, baseline; cps/mL, copies/mL; CAB, cabotegravir; DTG, dolutegravir; CVF, confirmed virological failure; InSTI, integrase stand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, 4-week dosing interval; RAMs, resistance-associated mutations, according to the IAS-US guidelines 2019 [43]; RPV, rilpivirine; SVF, suspected virological failure.
[a] BL RAMs were detected in peripheral blood mononuclear cell HIV-1 DNA for ATLAS and plasma HIV-1 RNA for FLAIR.
[b] The integrase polymorphism L74I was present in 6/7 participants at BL and in 5/7 participants at failure; this mutation is not considered an InSTI RAM by IAS-US guidelines and has no impact on CAB activity.
[c] Monogram biological cut-offs: RPV=2.0, CAB=2.5; Monogram clinical cut-off: DTG=4.0.

Table 3
ATLAS-2M study [5, 11, 13]: summary of virological failures and drug resistance

Dosing regimen	Sex	HIV-1 subtype[a]	CVF timepoint (Week)	Viral load at CVF (cps/mL)	BL RAMs[b] Major NNRTI	INSTI	CVF timepoint RAMs[c] Major NNRTI	INSTI	Drug sensitivity at CVF (fold change)[f] RPV	CAB
Q8W	Female	A	24	211 639	E138E/A	None[d]	**K101E**, E138A	**N155H**[d]	2.6	6.98
	Male	A1→A	48	296	None	None[d]	**E138E/K**[c]	**Q148Q/R, N155N/H**[d]	4.2	-
	Female	Complex→A	16	141 132	None	None[d]	**K101E**	**Q148R**[d]	4.7	9.1
	Male	B	16	737 830	None	None	None	None	1.4	0.6
	Male	B	24	5687	E138A, K103N, V108V/I	None	E138A, K103N	**N155H**	7.2	1.8
	Female	A1	24	16 205	Y188L, P225H	None[d]	Y188L, P225H	Analysis failed	15.0	-
	Female	C→Complex	8	267	V108V/I, Y181Y/C, H221H/Y	None	**K103N**[e]	None	2.4	1.1
	Female	C	16	938	Y188Y/F/H/L	G140G/R[d]	Y188L	**N155N/H, Q148Q/R**[d]	6.8	2.6
	Male	B	88	1916	K103N, Y181C	None[c]	K103N, Y181C	None	5.2	1.3
	Male	B	112	24 221	None	None	**E138A, M230M/L**	**Q148R**	-	-
	Male	A6[f]	120	59 467	None	None[d]	**E138A, Y181Y/C**	**Q148R**[d]	-	-
Q4W	Male	B	16	121 233	None	None	None	**N155N/H**	>119.2	1.8
	Male	B	32	9627	None	None	**K101E, M230L**	**E138E/K, Q148R**	17.0	4.6

In the table are reported participants with virological failure and emergent major resistance mutations (highlighted in bold). Underlined are reported the RPV major resistance mutations (K101E/P, E138A/G/K/Q/R, V179L, L100I, Y181C/I/V, Y188L, H221Y, F227C, M230I/L) resistance mutations reported in the IAS-US list [44].
Dash lines indicate that information is not available.
BL, baseline; cps/mL, copies/mL; CVF, confirmed virological failure; InSTI, integrase stand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; Q4W, 4-week dosing interval; Q8W, 8-week dosing interval; RAMs, resistance-associated mutations, according to the IAS-US guidelines 2019 [43]; SVF, suspected virological failure.
f Mutation observed in PBMCs (ATLAS study).
f Monogram biological cut-offs: RPV=2.0, CAB=2.5.
f This participant was originally classified as subtype A1 but, upon reanalysis, was later reclassified as subtype A6.
[a] The subtype labelling "Complex->A" and "C->Complex" refer to two cases where subtyping at baseline and at virological failure did not match, likely due to mosaic structures interpreted differently by the two separate analyses.
[b] BL RAMs were detected in peripheral blood mononuclear cell HIV-1 DNA.
[c] Virological failure mutations were assessed in plasma HIV-1 RNA at SVF timepoint.
[d] The integrase polymorphism L74I was present in 7/13 participants and in 5/13 at SVF; this mutation is not considered an InSTI RAM by IAS-US guidelines and has no impact on CAB activity.

der long-acting CAB + RPV treatment. InSTI resistance emerged in both participants with virological failure in the Q4W arm. Three additional virological failures occurred after week 48: one at week 88, with the same NNRTI resistance mutations detected at baseline and failure and without emergent InSTI resistance [13]; one at week 112 and one at week 120, with emergence of resistance for both NNRTI and InSTI [11].

Comparing overall findings at week 48, the rate of emergence of resistance appears to be similar for the oral and long-acting CAB + RPV combinations, thus indicating a comparable genetic barrier that is independent of the administration route. However, considering the high rates of treatment success across all trials and the limited number of patients included in the oral CAB + RPV study, the small sample size makes such analysis largely underpowered. Also, given the approval of CAB + RPV as the first, long-awaited, long-acting therapy, it is unlikely that additional data comparing oral and long-acting CAB + RPV will become available.

3. What factors predict virological failure?

The identification of factors associated with virological outcome is essential to inform appropriate patient selection. Although phase III studies of long-acting CAB + RPV (FLAIR, ATLAS, and ATLAS-2M) showed non-inferiority with respect to the oral standard of care, it is important to identify factors that may predispose a minority of participants to confirmed virological failure (CVF). Cutrell and colleagues [14] investigated factors involved in virological failure in the three abovementioned phase III trials. Several baseline factors were considered and those emerging as independent predictors of the week-48 outcome included HIV-1 subtype A6/A1, body mass index (BMI) ≥30 kg/m^2, and RPV-resistance-associated mutations. Notably, although the occurrence of at least two of these factors was associated with an increased risk of CVF, no single factor was sufficient per se. Regression analysis showed that week 8 RPV trough concentration was an additional predictor of virological failure; however, this parameter is not relevant for patient selection. Molina et al. [15] recently analysed the data from the 522 European patients from these trials and detected a very low rate of CVF (<1%). At least two of the three baseline factors associated with CVF mentioned previously were scored in 0.4% of the European subjects. The virological non-response, set as HIV-RNA ≥50 copies/mL, occurred in 0.8% of participants and 4.2% of subjects did not have virological data according to the intention-to-treat exposed (ITT-E) population analysis.

3.1. What is the significance of L74I and A6/A1 subtype?

One factor that initially appeared to be associated with CVF at 48 weeks was the L74I integrase polymorphism [4, 5, 6, 8]. Among the 14 individuals with CVF (3 in FLAIR, 3 in ATLAS, 8 in ATLAS-2M), 10 harbored this mutation and, in most of the cases (8/10), this was associated with HIV-1 sub-subtype A1. As this mutation is strongly correlated with the recently defined sub-subtype A6 [16], further analysis was performed to include the A6 sub-subtype reference based on the 20 June 2020 version of the Los Alamos National Laboratory research grade sequence library (http://www.hiv.lanl.gov/). In a pooled analysis of 1039 individuals enrolled in the phase III studies that evaluated factors associated with CVF through week 48, the prevalence of baseline L74I was analysed with respect to HIV-1 subtype [14]. Subtype B was the most common subtype (72.7%, n=755/1039) and was not associated with L74I. No participant with CVF had both subtype B and L74I (n=0/41), whereas four participants with CVF had subtype B alone (0.6%, n=4/714) without L74I. Most participants (88.3%, n=106/120) with HIV-1 subtype A6/A1 also had L74I; of those, 6.6% (n=7/106) had CVF, representing 53.8% (n=7/13) of participants with CVF in this analysis. Multivariable logistic regression model confirmed the role of subtype A6/A1 on CVF, but not that of L74I, due to the strong correlation between the two variables.

Given the apparent clustering of CVF with subtype A6/A1 and L74I, in vitro experiments were also conducted to determine the impact of L74I and subtype A6/A1 compared to subtype B on InSTI sensitivity [17–19]. One study performed on samples from the three FLAIR CVF cases showed that: (i) integrase from subtype A1 did not differentially impact CAB activity in vitro compared to subtype B; (ii) integrase +/- L74I did not impact CAB activity in vitro for either subtype A1 or subtype B; (iii) the in vitro replication kinetics did not differ between subtype B, subtype A +/- L74I; and (iv) subtype A1 integrase at baseline did not favor CAB resistance selection in vitro [17]. In the other study, recombinant viruses were generated that carried the A6 integrase region derived from 15 patients (14 of which had L74I) and all were shown to be fully susceptible to raltegravir, dolutegravir, bictegravir and CAB, except for 6 viruses with FC values associated with a possible minimal reduction in raltegravir susceptibility [18]. Thus, phenotypic susceptibility to InSTIs in subtype A6 does not appear to differ from that in subtype B. A recent study showed that L74I confers greater replication capacity to recombinant viruses expressing HIV-1 A6 integrase when present together with INSTI resistance mutations at positions 118, 140, 148 and 263. This finding may partly explain the association of HIV-1 subtype A6 and virological failure observed in clinical trials of CAB + RPV LA [19].

3.2. Most of the patients who failed had an A6/A1 viral subtype – should clinicians avoid using CAB + RPV LA in patients with this subtype?

Although the experiments mentioned above did not detect any advantage for A6 HIV in terms of susceptibility to CAB, further analyses may be advisable to test the role of A6 genetic background outside the integrase coding region to confirm whether or not sub-subtype A6 increases the risk of failure of InSTI-based therapy. The HIV-1 subtype A is uncommon in Western countries (<5%) but may be of greater importance in East and Central Africa, Eastern Europe, and Central Asia [20, 21], with sub-subtype A6 being the most prevalent lineage in some parts of Eastern Europe [16, 22]. Also, on-line systems discriminating sub-subtype A6 from A/A1 are not currently available; therefore, any treatment decision based on the HIV-1 lineage would be challenging in clinical practice. Overall, harboring a generic subtype A virus, particularly in the absence of any other risk factor, should not preclude the use of long-acting CAB + RPV therapy.

3.3. As RPV RAMs were a baseline factor associated with increased risk, how does this contribute to CVF? What about NNRTI class overall? In parallel, is archived resistance testing needed before using CAB + RPV LA?

The pooled analysis performed by Cutrell and colleagues showed that RPV-resistance-associated mutations (RAMs) detected in PBMCs at baseline before the switch to long-acting CAB + RPV are one of the factors statistically associated with CVF [14].

The presence of RPV RAMs in PBMCs was not known before enrolment in the ATLAS and ATLAS-2M trials and may reflect prior NNRTI exposure with underlying drug resistance, or transmitted drug resistance, which would cause reduced susceptibility to RPV. Although proviral RPV RAMs were associated with the greatest increase in the odds of CVF, the presence of only RPV RAMs does not seem to be sufficient to determine a CVF. In fact, in the pooled analysis, all 24 participants with baseline proviral RPV RAMs as their only factor associated with CVF maintained virological control. The analysis revealed that at least two factors are required to predict CVF. Notably, in the same analysis, the presence of NNRTI RAMs at baseline, once those specifically associated with RPV are excluded, was not significantly associated with increased odds of CVF [14]. Overall, past RPV resistance, although not sufficient *per se* to cause virological failure, remains a biologically plausible driver of lower treatment response. Indeed, prescribing information for long-acting CAB + RPV explicitly recommends excluding these cases. Within the large list of mutations that account for NNRTI resistance (https://hivdb.stanford.edu/dr-summary/resistance-notes/NNRTI/ and https://www.iasusa.org/resources/hiv-drug-resistance-mutations/), only a subset can impact response to RPV, including L100I, K101E/P, E138A/G/K/Q, Y181C/I/V, Y188L, G190E, and M230L. Importantly, the list does not include K103N, typically selected in patients failing NVP- and EFV-based therapies and by far the most common transmitted NNRTI resistance mutation. The occurrence of RPV-resistance-mutations in ART-naïve subjects is below 0.1% [23], except for E138A, which is reported with varying degrees of RPV resistance by all three major algorithms: ANRS

reports full resistance, Stanford reports low level resistance, and Rega reports intermediate resistance. Indeed, E138A is a natural polymorphism occurring in 2.6% of all the sequences from NNRTI individuals stored in the Stanford database, with uneven distribution among subtypes (from 0.3% in CRF01_AE to 5.5% in subtype C). The decrease in RPV susceptibility in vitro for the E138A mutant is around 2-fold [24]. In a few virologically-suppressed subjects switching to RPV + tenofovir/emtricitabine, the presence of E138A at baseline did not lead to virological failure [25]. E138A has been shown to decrease the genetic barrier to resistance to etravirine in vitro [26] but similar experiments with RPV have not been performed.

Historical genotypic resistance testing (GRT) should generally be checked before prescribing long-acting CAB + RPV and the treatment should be avoided in individuals harboring RPV-resistant variants. When no past GRT is available in NNRTI-naïve individuals, RPV is likely to be effective but there may be exceptions. In these cases, GRT on peripheral blood DNA could be considered when another known risk factor (e.g., obesity) is present, and RPV administration should be avoided if there is evidence of RPV resistance. One technical limitation is the lack of commercially available kits for HIV-1 genotyping from blood DNA. Also, the retrieval of past GRT results in patient charts may not always be feasible, e.g., because the patient has moved to a different clinic. The role of RAMs detected in PBMC DNA, compared with routine plasma RNA, is uncertain [27] and there is no evidence that RPV resistance in DNA per se predicts future failure of long-acting CAB + RPV. For these reasons, HIV-1 DNA genotypic resistance testing is not recommended as a strategy for screening patients who are going to receive this drug combination.

3.4. Can we use CAB + RPV LA in patients with high BMI?

The presence of at least two of the following three factors, BMI $\geq$30kg/m^2, proviral RPV RAMs or HIV-1 subtype A6/A1 was associated with an increased risk of virological failure at 48 weeks in three randomized clinical trials (FLAIR, ATLAS, and ATLAS-2M) [14]. The presence of all three factors was detected in only one subject, who experienced virological failure. In this multivariable analysis, high BMI alone was not associated with virological failure.

Among the two virological failures in the FLAIR trial at 124 weeks, only one occurred in a subject with BMI $\geq$30kg/m^2, together with plasma concentrations of CAB and RPV under the 5th percentile [28]. A BMI $\geq$30kg/m^2 is often a proxy of an increased amount of adipose tissue, possibly resulting in decreased drug release if these long-acting compounds are not injected into the muscle. This potential issue is related not only to operator expertise but also to the organization of outpatient facilities. For example, obesity is also associated with an increase in subcutaneous adipose tissue, which should be managed by selecting the appropriate needle length for intramuscular injections (2 inches, i.e., 5.08 cm, for subjects with BMI >30 kg/m^2 and 1.5 inches, i.e., 3.81 cm, for subjects with BMI <30 kg/m^2).

In a recent analysis, the efficacy and safety of the long-acting CAB + RPV combination was evaluated in phase III/IIIb trials according to different BMI categories through week 48 [29]. In the ITT-E population, 59 subjects in the Q8W schedule and 154 subjects in the Q4W schedule had BMI $\geq$30kg/m^2, which corresponds to a total of 7% of subjects. CVF occurred in 8 of these subjects, each of whom had at least one other baseline factor (3 RPV RAMs, 4 subtype A6/A1, 1 both), whereas there were no reports of CVF in subjects with BMI $\geq$30kg/m^2 as the only baseline factor. In parallel, the 48-week analysis of US and Canadian patients enrolled in the same phase III/IIIb clinical trials (ATLAS, FLAIR, and ATLAS-2M) revealed that 26% of subjects had BMI $\geq$30kg/m^2 and three individuals met the criterion for CVF. None of the 79 subjects with BMI $\geq$30kg/m^2 as the only baseline factor had a CVF [30].

4. Which patients are most appropriate for a long-acting therapy?

Most people living with HIV with <50 HIV-RNA copies/mL are eligible to receive the long-acting cabotegravir-rilpivirine (CAB + RPV) regimen. Hence, this regimen should be considered for all adult PLWH, regardless of age, sex, and risk factor for HIV.

However, prescribers should be cautious about offering this regimen in some circumstances. The main reason to avoid long-acting CAB + RPV is present or past evidence of viral resistance or prior virological failure to NNRTIs or InSTIs because these conditions can increase the risk of failure to CAB and RPV. Other settings in which long-acting CAB + RPV should be avoided include chronic hepatitis B virus (HBV) co-infection, history of intolerance or toxicity to InSTIs or RPV, concomitant use of drugs known to prolong the QT interval or strong inducers of the CYP3A fraction of the p-450 cytochrome (e.g., rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenytoin or phenobarbital, systemic dexamethasone, St John's wort/Hypericum perforatum).

Furthermore, prescribers should be cautious when considering this regimen for patients who find it difficult to regularly attend programmed visits. Tail concentrations of these drugs are not high enough to guarantee virological suppression for a long time beyond the next scheduled injection, which entails a higher risk of selecting drug-resistant variants [31]. However, this limitation can be viewed as an opportunity to develop systems to control and correct adherence issues, i.e., a recall system or a reminder a few days before the scheduled visit date. The delay in therapy has been modeled for both CAB and RPV [32, 33] and the summary of product characteristics reports the indication for managing missed doses for monthly or bi-monthly CAB + RPV administration. As stated by the Department of Health and Human Services (DHHS) guidelines in November 2021 (https://clinicalinfo.hiv.gov/en/guidelines), the occurrence of missed doses (beyond the 7-day window) should prompt re-evaluation of whether the individual remains an appropriate candidate for this long-acting therapy. If injections are missed by more than 2 months and the regimen is re-initiated, administration should be resumed with a loading dose followed by monthly maintenance dosing. When stopping therapy, transition to a suppressive oral regimen should be undertaken within 4 weeks of the last intramuscular dose.

For pregnant or breastfeeding women, individuals receiving anticoagulants, or those with very high BMI, severe thrombocytopenia, uncontrolled depression, severe liver insufficiency, or history of allergy to nevirapine or efavirenz, the indication to this regimen should be carefully evaluated and balanced with available alternatives. CAB concentrations were measured during pregnancy and post-partum in 3 women with HIV infection who became pregnant while participating in studies with long-acting CAB + RPV [34]. After discontinuation of CAB, residual CAB concentrations remained measurable throughout pregnancy in 2/3 women and were around 0.5 µg/mL, a level equivalent to 3 × protein-adjusted IC90 (PA-IC90 = 0.166 µg/mL), at the time of delivery. CAB remained measurable post-partum (range: 2-23 weeks) in 2/3 women.

5. The need for an oral lead-in phase

The FDA (https://www.hiv.gov/topics/fda) and DHHS (https://clinicalinfo.hiv.gov/en/guidelines) currently recommend CAB and RPV injections are preceded by oral lead-in. However, it has recently been proposed that switching to this long-acting regimen had similar safety, tolerability, and efficacy with or without an oral lead-in phase [10]. Although the direct-to-injection strategy has

not been investigated in a randomized clinical trial, the results of the extension phase of the FLAIR study indicate that the oral lead-in phase does not improve the tolerability of the long-acting regimen in PLWH receiving dolutegravir at the time of switching to injection. These results are not surprising as only 1.5% of people interrupted the oral lead-in therapy in the initial phase of both the FLAIR and ATLAS studies. Unfortunately, data for this strategy are available only for individuals receiving dolutegravir-based regimens. However, the results of the extension phase of the FLAIR study strongly indicate that it is worth exploring further the possibility of switching directly to injection in people on-treatment with any InSTI, in those receiving oral RPV and even when the regimen of origin includes only drugs other than InSTIs or RPV. This issue is in part under investigation in the ongoing SOLAR trial [NCT04542070]. If the oral lead-in was also shown to be non-essential in individuals receiving regimens that are not based on dolutegravir, this would simplify the adoption of long-acting CAB and RPV.

6. Conclusions and perspectives

The feasibility of long-acting CAB + RPV administration has recently received considerable attention. Results from the CUSTOMIZE trial, presented at IAS 2021, showed the successful implementation and efficacy of this treatment during the COVID-19 pandemic. Most patients and staff perceived a high rate of feasibility and satisfaction during the trial [35]. Data from the European CARISEL implementation-effectiveness study showed improved treatment satisfaction for enrolled subjects [36] and the study staff reported a high degree of acceptability, appropriateness, and feasibility at study months 1 and 5 [37]. Drug ordering, stock, and supply chain are three of the many issues associated with oral lead-in and injectable administration. Further issues include identifying candidates for injectable ART, counseling and supporting the oral lead-in phase, scheduling and counseling for initial injections and follow-up sessions, staffing initial and follow-up sessions, tracking patient schedules, sending reminders, outreach if treatment is late, and prescribing oral medicines if there is a long gap between doses. A cell phone app that tracks the patients' calendars is a potential solution; however, interfacing with the hospital systems may be difficult because of security constraints.

The management of PLWH treated with long-acting agents involves many practical issues. Involvement of an infectious diseases specialist rather than a general practitioner may result in higher virological success rates. Thus, the patient's selection for long-acting CAB + RPV treatment is easier but the logistical organization of outpatient clinics remains a pivotal point.

The one-million-dollar question is: will our patients be as enthusiastic about long-acting CAB + RPV as their doctors? Lifestyle considerations with our patients will be a good place to start the process. Also, reorganizing outpatient clinics is essential for introducing long-acting CAB + RPV into the clinic. A web-based survey was conducted in June 2016 by the Italian non-governmental organization (NGO), Nadir Onlus [38]. A total of 488 PLWH completed the survey: 268 (55%) respondents knew about upcoming long-acting regimens, 408 (83%) appreciated the idea of not taking ART every day, 336 (69%) declared that the greatest benefit would be not having to remember to take the pills – so feeling "more free", and 402 (83%) felt better with the idea of an injection every two months. It would be interesting to conduct such a survey again, more than 5 years later, with the additional information now available to patients and clinicians. A recent survey was conducted in 486 subjects (Gianotti N, personal communication) on attitudes towards long-acting CAB + RPV. Three hundred and twenty-five (67%) individuals were interested, 91 (19%) were undecided, and 70 (14%) were not interested. Multivariable analysis showed that PLWH under an NNRTI-based or a PI-based regimen were less favorable to switching to long-acting CAB + RPV, compared with PLWH under an INSTI-based regimen. Another recent survey among PLWH reported that young age, recent HIV diagnosis and disclosure issues were associated with a higher interest in long-acting regimens [39]. The 2019 Positive Perspectives survey (n=2389) analyzed treatment preferences in European (n=969) vs. non-European (n=1420) participants. Preference for long-acting agents was similar between European (54.4% [527/969]) vs. non-European participants (54.9% [779/1420]), nevertheless non-European participants reported significantly higher suboptimal adherence (29.5% vs. 16.1%; $p<0.05$), stress from daily dosing (35.6% vs. 29.8%; $p<0.05$), and difficulty swallowing (38.3% vs 25.4%; $p<0.05$) [40].

Based on large and extended clinical trials, there is strong evidence of the efficacy of long-acting CAB + RPV. The causes and consequences of CVF remain uncertain, mostly because of the very few events so far. The future efficacy and safety of this promising combination relies on the expertise of virologists and clinicians and their capacity to find the right answer to the right question – no short-cut is allowed. The management of these long-acting compounds will involve practical challenges that require innovative solutions.

Ethical Approval

Not required.

Sequence Information

Not applicable

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Declaration of Competing Interest

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