OTTIMIZZAZIONE DELLA ART

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OTTIMIZZAZIONE HAART
Definizione

“ …. strategie finalizzate al miglior risultato possibile, attraverso cambiamenti dei regimi terapeutici anche differenti fra loro e con diversi scopi e razionali ma sempre in condizioni di soppressione virologica”

“Una terapia antiretrovirale ottimale non necessariamente presuppone una riduzione del numero di compresse o dosi …

Il limite delle terapie antiretrovirali di combinazione (ART) attualmente disponibili consiste nell'impossibilità di ottenere l'eradicazione dell'infezione: il trattamento deve quindi essere continuato a tempo indefinito ed è probabile che, per motivi differenti (tossicità, invecchiamento, comorbilità, prevenzione di danni d'organo, interazioni farmacologiche, ridotta aderenza), nel corso degli anni si rendano opportune modifiche al regime in atto, anche in assenza di fallimento virologico.

Ragioni di Ottimizzazione

- Intolleranza (effetti indesiderati, documentata tossicità)
- Regime in atto che possa aggravare comorbosità preesistenti
- Prevenzione di tossicità a lungo termine (pre-emptive switch)
- Regime in atto non più raccomandato
- Interazioni con altri farmaci (TB, HBV, HCV)
- Necessità di migliorare l'aderenza alla terapia del paziente
- Pianificazione della gravidanza
- Richiesta di paziente

Reason to consider ART SWITCH during viral suppression

Appropriate

- To **simplify** a regimen by reducing pill burden and/or dosing frequency
- To enhance **tolerability** and/or decrease short- or long-term **toxicity**
- To prevent or mitigate **drug-drug interactions**
- To eliminate food or fluid requirements
- To allow for optimal use of ART **during pregnancy** or in cases where pregnancy may occur
- To **reduce costs**

Inappropriate

- To use the "newest" regimen
- To reduce costs at the price of a toxicity or intolerance risk for your patient

DHHS Guidelines. Dec 2022.

Il termine ottimizzazione della ART è utilizzato in queste linee guida per indicare strategie finalizzate alla miglior salute psico-fisica del paziente, attraverso modifiche al regime terapeutico in atto, con finalità differenti, ma sempre in condizioni di soppressione virologica (HIV-RNA <50 copie/mL).

Le principali finalità di un'ottimizzazione terapeutica sono:

- Ovviare a una tossicità in atto (switch reattivo);
- Prevenire una tossicità prevedibile (switch preventivo o proattivo);
- Favorire l'aderenza attraverso una riduzione in sicurezza del numero di compresse o di dosi;
- Ovviare a interazioni farmacologiche sfavorevoli.

A volte non è possibile definire a priori come modificare un regime in presenza di tossicità o di interazioni farmacologiche: in questi casi il curante dovrà valutare caso per caso le modifiche da apportare, tenendo presente che devono essere sempre accuratamente valutati, bilanciati e discussi con i pazienti i potenziali rischi e i benefici degli schemi di trattamento alternativi al regime in atto.

Gli schemi terapeutici dovranno rappresentare comunque la cornice di riferimento e ogni modifica del regime deve sempre avere le seguenti priorità:

- Mantenere la soppressione virologica;
- Garantire con ragionevole certezza che i potenziali benefici per il paziente siano superiori ai potenziali rischi (lo switch deve essere un vantaggio per il singolo paziente).

L’attenzione a queste due priorità dovrebbe essere estrema in caso di switch preventivo o finalizzato alla riduzione delle dosi/compresse.

In generale, è anche necessario tenere presente che dalla maggior parte degli studi clinici di switch sono stati esclusi pazienti con precedenti fallimenti virologici o documentata presenza di farmacoresistenze: prima di modificare il regime in atto è quindi necessaria un’attenta revisione della storia terapeutica e della cartella clinica, con particolare attenzione ai precedenti fallimenti (anche a regimi subottimali con NRTI) e ai risultati dei precedenti test di farmacoresistenza;

soprattutto, dovrà essere posta estrema attenzione al contesto clinico in cui si propone al/la paziente lo switch da un regime ad alta barriera genetica a un regime a bassa barriera genetica.

Il termine STR (single tablet regimen) definisce una combinazione a dose fissa (FDC, fixed dose combination), in una singola compressa, di un regime antiretrovirale completo, in alternativa a MDR (multiple tablet regimen) che indica regimi di terapia a più compresse.

La riduzione massima della terapia permette un ottimo adattamento a qualsiasi stile di vita, in quanto tutta la terapia può essere assunta in una singola compressa quotidiana e risponde alla preferenza della maggior parte dei pazienti

Regimi raccomandati in switch DHHS 2022

Dolutegravir plus Rilpivirine

Two Phase 3 trials enrolled 1,024 participants with viral suppression for ≥1 year (defined by no HIV RNA >50 copies/mL in the past 6 months, and no more than one instance of HIV RNA 50 to 200 copies/mL in the 6 to 12 months before enrollment) who were on their first or second regimen, had no history of virologic failure, and no documented evidence of any major drug-resistance mutations.[23] Participants were randomized to remain on their combination ARV regimen or to switch to a regimen of once-daily DTG plus RPV (early-switch arm). Viral suppression was maintained in 95% to 96% of the participants in both arms at 48 weeks. At 52 weeks, those who were randomized to remain on their current regimens were allowed to switch to DTG plus RPV (late-switch arm). At 100 weeks, 89% of participants in the early-switch arm and 93% of those in the late-switch arm maintained HIV RNA <50 copies/mL.[24] DTG plus RPV is available as a coformulated single-tablet regimen and is a reasonable option when the use of NRTIs is not desirable. DTG plus RPV should be given only to patients who do not have chronic HBV infection (unless the patient is also on an HBV active regimen), have no evidence of resistance to either DTG or RPV, and have no significant drug-drug interaction that might reduce the concentration of either drug **(AI)**.

Dolutegravir plus Lamivudine or Emtricitabine

A switch from three-drug regimens to DTG plus (3TC or FTC) as maintenance strategy in patients with virologic suppression has been examined in a large randomized clinical trial (TANGO),[25] in three small clinical trials,[26, 27] and in observational studies[28-30] with good success.

Regimi raccomandati in switch DHHS 2022

Ritonavir-Boosted Protease Inhibitor plus Lamivudine

A ritonavir-boosted protease inhibitor (PI/r) plus 3TC may be a reasonable option when the continued use of TDF, TAF, or ABC is contraindicated or not desirable. Growing evidence indicates that a PI/r-based regimen plus 3TC can maintain viral suppression in patients who initiated triple-drug therapy, achieved sustained viral suppression for ≥1 year, and have no evidence of or risk for drug resistance to either the PI/r or 3TC. However, these regimens have a higher pill burden and are less well tolerated than the above-mentioned dual combinations. These regimens are not suitable for individuals with active HBV infection, unless the patient is also on an HBV active regimen. To date, no published clinical trials have evaluated cobicistat-boosted PI with 3TC as dual therapy, but clinically, these regimens are reasonable. Examples of boosted PI plus 3TC regimens that have been shown to be effective in clinical trials include the following:

- ATV/r plus 3TC **(CI)**[31, 32]
- Darunavir/ritonavir (DRV/r) plus 3TC **(BI)**[33]
- LPV/r plus 3TC **(CI)**[34]

Boosted Darunavir plus Dolutegravir

An open-label, Phase 3b, non-inferiority clinical trial randomized 263 participants who were on boosted DRV plus two NRTIs to continue on the same regimen or switch to boosted DRV plus DTG (study recruitment was stopped prematurely due to slow recruitment). At 48 weeks, the study demonstrated that switching to DTG plus boosted DRV was non-inferior to continuing triple therapy. In both arms, approximately 87% of participants maintained

Switch strategies for virological suppressed person

Definition of virologically suppressed

Clinical trials exploring switching strategies have generally defined suppression as an HIV-VL < 50 copies/mL for at least 6 months

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen, see Adverse Effects of ARVs and Drug Classes
2. **Prevention of long-term toxicity**, see Adverse Effects of ARVs and Drug Classes. This may include person's concerns about safety
3. **Avoidance of drug-drug interactions,** page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see Drug-drug Interactions between Viral Hepatitis Drugs and ARVs
4. **Planned pregnancy or women wishing to conceive,** see Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy
5. **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification**: to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification**: Increasing the barrier to resistance of a regimen in order to prevent VF (e.g. in persons with reduced adherence)
9. **Cost reduction:** switching to the generic form of their current regimen, if available

Switch strategies for virological suppressed person

Principles

11. If a PLWH receives and tolerates a regimen that is no longer a preferred option, and none of the other reasons for change applies, there is no need to change. Example: persons tolerating EFV-containing regimens

Riassunto novità EACS

- Doravirina entra come raccomandata
- Rimossi i regimi I linea con EVG e ATV; RAL e RPV rimangono solo in alternative in triplice terapia. DRV boosterato solo come alternativa in triplice
- CAB +RPV long acting sono entrati esclusivamente in switch
- ATV/r+3TC è uscito dalle strategie di switch.

Nuovi antiretrovirali

Antiretroviral class	Leading candidates	Route of administration
Attachment inhibitor	Fostemsavir	**Oral**
Anti-CD4 monoclonal antibodies	Ibalizumab	**Intravenous infusion**
Capsid inhibitors	Lenacapavir	**Oral, Subcutaneous injection**
Fusion inhibitors	Albuvirtide	Intravenous injection
Integrase strand-transfer inhibitor (INSTI)	Cabotegravir (with NNRTI, rilpivirine)	**Oral, Intramuscular gluteal injection**
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Elsulfavirine (*under investigation*)	Oral
Nucleoside reverse transcriptase translocation inhibitors (NRTTIs)	Islatravir	Long-acting oral, implant, Intravenous injection
Maturation inhibitors	GSK 2838232 (*under investigation*)	Oral

La novità più grande…

CAB and RPV IM injections can be used as an optimization strategy for people receiving ART with **documented viral suppression for ≥3 mo** (AI) who:

- Have no baseline resistance to either medication
- Have no prior virologic failures
- Do not have active HBV infection (unless receiving an oral HBV active regimen)
- Are not pregnant or planning on becoming pregnant
- Are not receiving medications with significant drug interactions with oral (during lead-in or bridging therapy) or injectable CAB or RPV

Additional key considerations

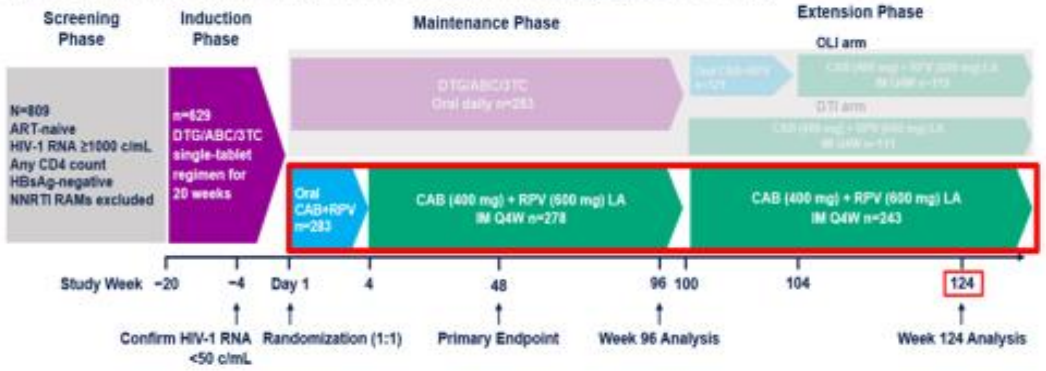
- Potential advantages of switching to LA ART include reducing pill fatigue, disclosure concerns, or stigma associated with taking daily oral medications and improving QoL

FLAIR Week 124: Study Design and Endpoints

- FLAIR (NCT02938520), a Phase 3, randomized, multicenter, open-label study, demonstrated noninferiority of switching virologically suppressed participants from daily oral dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) to monthly IM CAB + RPV LA over 96 weeks.
  - Results for participants switching from DTG/ABC/3TC to CAB + RPV LA (with or without an oral lead-in) were previously presented[1]
- Endpoints at Week 124 included the proportion of participants with HIV-1 RNA ≥50 and <50 copies/mL (FDA Snapshot), confirmed virologic failure (CVF; two consecutive viral loads ≥200 copies/mL), and safety and tolerability

Baseline Characteristics and Participant Disposition*	Randomized CAB + RPV LA n=283†
ITT-E population	
Age, median (IQR) years	34 (29–42)
Female (sex at birth), n (%)	**63 (22)**
Female (self-reported gender), n (%)	65 (23)
Race, n (%)	
White	216 (76)
Black or African American	47 (17)
Other	20 (7)
Hispanic or Latinx ethnicity (%)	28 (10)
Body mass index, median (IQR) kg/m^2	24 (22–27)
CD4+ cell count, median (IQR) cells/mm^3	624 (473–839)

Phase 3, Randomized, Multicenter, Parallel-Group, Noninferiority, Open-Label Study*



*The study design figure has been adapted from Orkin C, et al. *N Engl J Med* 2020;381:1124–1135 and Orkin, et al. *Lancet HIV* 2021;8(4):e185–e196. †Data collected at maintenance baseline (Day 1).

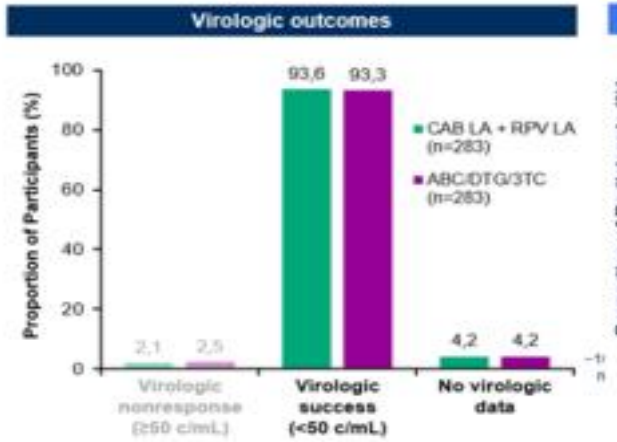
3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; CAB, cabotegravir; CVF, confirmed virologic failure; DTI, direct-to-injection; DTG, dolutegravir; FDA, Food and Drug Administration; HBsAg, hepatitis B surface antigen; IM, intramuscular; LA, long-acting; NNRTI, non-nucleoside reverse transcriptase inhibitor; OLI, oral lead-in; Q4W, every 4 weeks; RAM, resistance-associated mutation; RPV, rilpivirine.

1. D'Amico R, et al. Glasgow HIV 2020;O414

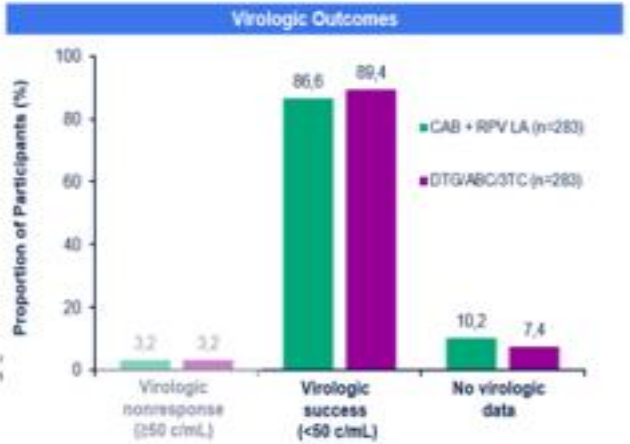
Orkin C et al. IAS 2021; Virtual. Presentation OAB0302.

FLAIR Virologic Snapshot Outcomes Overall Summary

at Week 48 for ITT-E



at Week 96 for ITT-E



FLAIR Week 124: Safety Overview (Excluding ISRs) and ISR Summary

	CAB + RPV LA (Cumulative through Week 124) (n=283), n (%)	Additional participants since Week 96 data analysis n (%)
Any AE	271 (96)	7 (2)
Grade 3 to 4 AEs	38 (13)	9 (3)
Drug-related AEs	102 (36)	7 (2)*
Drug-related Grade 3 to 4 AEs	5 (2)	1 (<1)
AEs leading to withdrawal	**15 (5)**	**1 (<1)†**
Any SAE	33 (12)	2 (1)
Drug-related SAEs	**1 (<1)‡**	**0**
Fatal SAEs	0	0
Drug-related AEs (>3%)§		
Pyrexia	18 (6)	1 (<1)
Headache	15 (5)	0
Fatigue	10 (4)	3 (1)

only one drug-related Grade 3/4 AE occurred since the Week 96 analysis (paracetamol overdose, Grade 3)

- There were **no confirmed drug-related hypersensitivity reactions from baseline through 124 weeks** and there was one additional case of liver stopping criteria being met since the Week 96 analysis¶

Outcome, n (%)	CAB + RPV LA n=283
Number of injections	17,392
ISR events	3732 (21%)
Pain, n (% of total injections)	3131 (18)
Nodule, n (% of total injections)	**162 (<1)**
Indurations, n (% of total injections)	**158 (<1)**
Median duration of ISRs, days	3
Participants who withdrew due to ISR-related reasons, n (% of participants)‖	7 (2)

*Three most common ISRs

*Seven participants reported 22 events since the Week 96 analysis (pyrexia n=1, fatigue n=3, chills n=2, influenza-like illness n=1, paresthesia n=1, autonomic nervous system imbalance n=1, hypoesthesia n=1, lethargy n=1, restless leg syndrome n=1, nausea n=1, blood creatine phosphokinase increased n=1, myalgia n=1, back pain n=1, erythema n=1, syphilis n=1, dyspnea n=1, cough n=1, flushing n=1, overdose n=1. †Paracetamol overdose. ‡Drug-related SAE was right knee monoarthritis reported in the Week 48 analysis. §Drug-related AEs are based on investigator assessment. ¶Secondary syphilis; not drug related. ‖Participants who withdrew due to ISR-related reasons included participants with injection intolerability (n=4) and those who had ISRs leading to withdrawal (n=3). AE, adverse event; CAB, cabotegravir; ISR, injection site reaction; LA, long-acting; RPV, rilpivirine; SAE, serious adverse event.

Orkin C et al. IAS 2021; Virtual. Presentation OAB0302.

FLAIR Conclusions

- Monthly CAB LA + RPV LA was noninferior vs continued oral ABC/DTG/3TC at Week 48 per Snapshot
  - Low rate of HIV-1 RNA ≥50 c/mL: 2.1 vs 2.5%
  - HIV-1 RNA <50 c/mL: 93.6% vs 93.3%
- Low CVF rate across both treatment arms: 1.4% vs 1.1%
  - Three participants on CAB LA + RPV LA had treatment-emergent resistance for NNRTI and INSTI at CVF
  - No resistance emerged in the ABC/DTG/3TC arm
- ISRs in the LA arm were common but mainly grade 1 or 2; their incidence decreased markedly over time with few associated discontinuations
- Grade 3+ and serious AEs were infrequent in both treatment arms
- Participants receiving CAB LA + RPV LA reported a significantly greater increase in treatment satisfaction vs prior treatment than those receiving ABC/DTG/3TC at Week 48
- These results suggest monthly CAB LA + RPV LA is an effective option for maintaining viral load suppression in individuals previously treated with a short course of oral induction therapy

3TC, lamivudine; ABC, abacavir; AE, adverse event; CAB, cabotegravir; CVF, confirmed virologic failure; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; ISR, injection site reaction; LA, long-acting; NNRTI, non-nucleoside RTI; RPV, rilpivirine.

Orkin C, et al. *CROI 2019*; Seattle, WA. Abstract 3947.

ATLAS Background

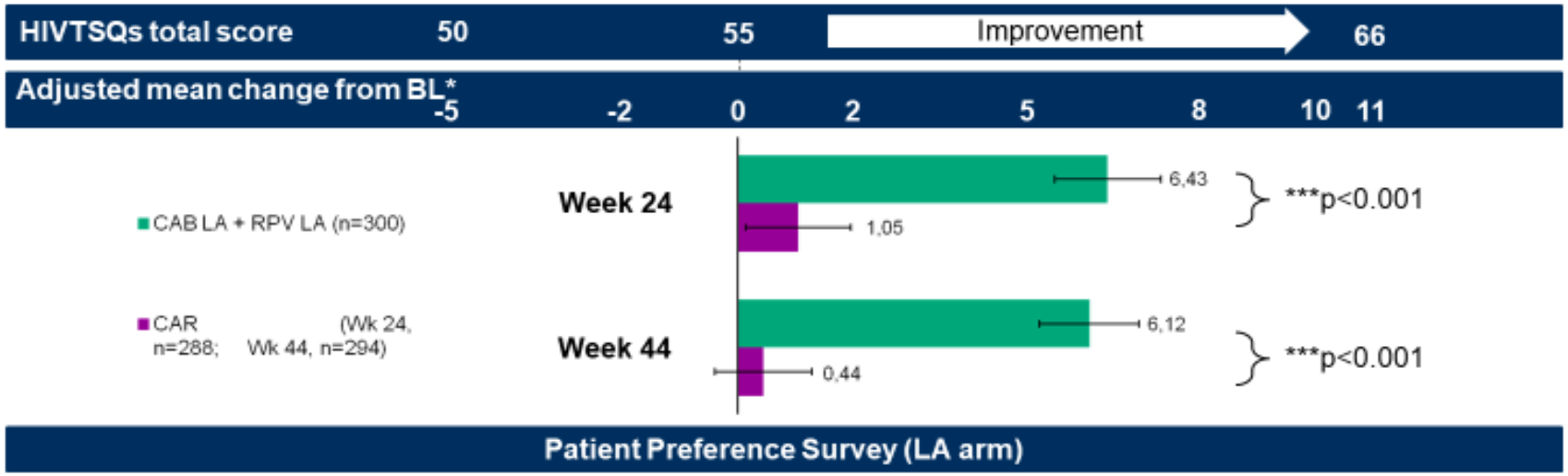
- HIV therapy has been simplified to once-daily, oral regimens containing 2 or 3 antiretrovirals
- Despite the success of daily oral therapy, considerable interest exists in LA injection treatment options
- Cabotegravir (CAB) is an HIV-1 integrase strand transfer inhibitor
  - Oral 30 mg tablet: $t_{½}$ ~40 hours
  - LA IM injection, 200 mg/mL: $t_{½}$ ~40 days
- Rilpivirine (RPV) is an HIV-1 non-nucleoside reverse transcriptase inhibitor
  - Oral 25 mg tablet: $t_{½}$ ~50 hours
  - LA IM injection, 300 mg/mL: $t_{½}$ ~90 days

- LATTE-2: CAB LA + RPV LA given every 4 or 8 weeks maintained HIV-1 RNA <50 c/mL for >3 years[1]
- Two pivotal phase 3 studies (ATLAS and FLAIR[2]) have reached their primary endpoints at 48 weeks

CAB, cabotegravir; IM, intramuscular; LA, long-acting; RPV, rilpivirine; t½, half-life.
1. Margolis D, et al. HIV Glasgow 2018; UK. Poster 118; 2. Orkin C, et al. CROI 2019; Seattle, WA. Abstract 3947.

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.

ATLAS: High Participant Satisfaction (HIVTSQs) and Preference For Injectable Therapy



NP-IT-CBR-PPT-220005

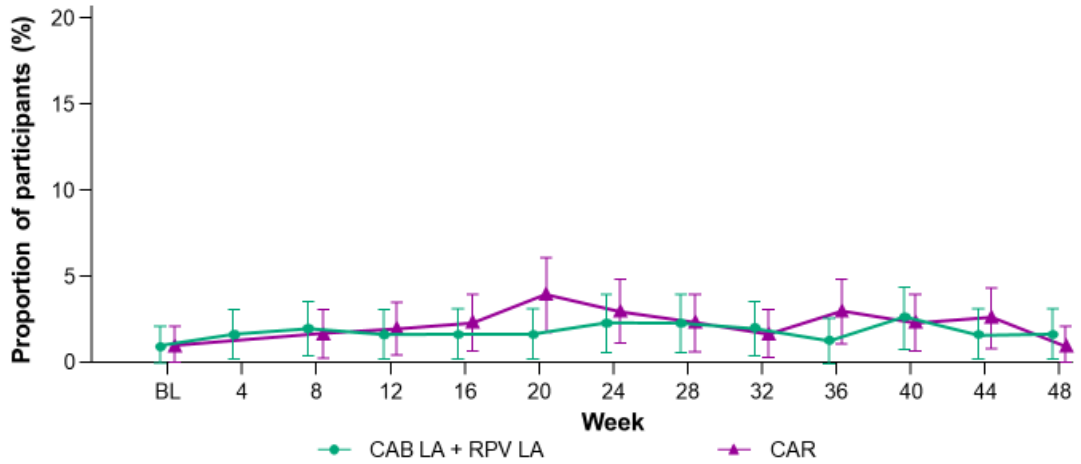
Patient Preference Survey (LA arm)

- Single-item question on participants' preference at Week 48:
  - ITT-E population: 266 of 308 (86%) preferred LA; 7 of 308 (2%) preferred daily oral therapy
  - Responding participants: 266 of 273 (97%) preferred the LA regimen over previous oral therapy

BL, baseline; CAB, cabotegravir; CAR, current ART; HIVTSQs, HIV Treatment Satisfaction Questionnaire - status; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.
*Adjusted for baseline score, sex, age, race, and baseline third agent class. Error bars show 95% confidence interval.

Swindells S, et al. *CROI 2019*; Seattle, WA. Abstract 1475.

ATLAS Primary Endpoint (HIV-1 RNA ≥50 c/mL) by Snapshot Analysis at Week 48 for ITT-E



BL, baseline; CAB, cabotegravir; CAR, current ART; ITT-E, intention-to-treat exposed; LA, long-acting; RPV, rilpivirine.

Swindells S, et al. CROI 2019; Seattle, WA. Abstract 1475.

ATLAS Conclusions

- Monthly CAB LA + RPV LA was noninferior to 3-drug oral CAR at Week 48 per Snapshot
  - Low rate of HIV-1 RNA ≥50 c/mL: 1.6% vs 1.0%
  - HIV-1 RNA <50 c/mL: 92.5% vs 95.5%
- Low CVF rate (1%) across both treatment arms
  - Two of three participants on CAB LA + RPV LA had NNRTI RAMs in baseline PBMCs
- ISRs were mostly grade 1 or 2 and short-lived with few associated discontinuations
- Grade 3/4 and serious AEs were infrequent in both treatment arms
- Significantly greater increase in treatment satisfaction reported with LA regimen over time vs CAR
- Overall, these results support the therapeutic potential of monthly CAB LA + RPV LA

AE, adverse event; CAB, cabotegravir; CAR, current ART; CVF, confirmed virologic failure; ISR, injection site reaction; LA, long-acting; NNRTI, non-nucleoside RTI; PBMC, peripheral blood mononuclear cell; RAM, resistance-associated mutation; RPV, rilpivirine.

Swindells S, et al. *CROI 2019*; Seattle, WA. Abstract 1475.

ATLAS-2M Week 48 Conclusions

- **Q8W dosing of CAB + RPV LA was highly efficacious and noninferior to Q4W dosing**
  - Virologic non-response (≥50 c/mL) was infrequent and similar between the two arms
  - Virologic suppression was maintained in 94.3% and 93.5% of those in the Q8W and Q4W arms, respectively
  - The rate of confirmed virologic failure was low overall (1%)
- **CAB + RPV LA was well tolerated with a comparable safety profile between arms**
  - ISRs were mostly Grade 1–2 (98%) with a median duration of 3 days
- **98% of participants preferred Q8W dosing of CAB + RPV LA treatment over oral therapy, and Q8W dosing was preferred by 94% of participants with prior Q4W experience**
- **CAB + RPV LA, dosed every 2 months, is an innovative and effective treatment for maintenance of virologic suppression in people living with HIV**

Overton et al. CROI 2020; Boston, MA. Presentation 34.

WEEK 96 EFFICACY AND SAFETY OF LONG-ACTING CABOTEGRAVIR + RILPIVIRINE EVERY 2 MONTHS: ATLAS-2M

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Disclosure: *Counselling, speaker's fees, and research support from ViiV Healthcare, Gilead, and MSD

ATLAS-2M Week 96: Conclusions

- **Both dosing regimens of CAB + RPV LA maintained high levels of virologic suppression (Q8W 91%; Q4W 90%),** with few participants having HIV-1 RNA ≥50 c/mL (Q8W, 2%; Q4W, 1%) at Week 96, demonstrating noninferiority of Q8W vs. Q4W dosing
  - The rate of **CVF** was low overall (**n=11/1045 [1%]**), with only one participant (Q8W arm) meeting the criterion in the second year of therapy
- CAB + RPV LA was **well tolerated with a comparable safety profile between arms**
  - No new safety signals were identified since the Week 48 analysis
  - ISRs were mostly Grade 1–2 (99%), short lived (median 3 days), and decreased in incidence over time
- These longer-term efficacy, safety, and tolerability data support CAB + RPV LA dosed monthly or Q2M as a complete regimen for the maintenance of HIV-1 virologic suppression in adults

CAB, cabotegravir; CVF, confirmed virologic failure; FDA, U.S. Food and Drug Administration; ISR, injection site reaction; LA, long-acting; Q2M, every 2 months; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Considerazioni pratiche per CAB/RPV im

Practical Considerations When Using Long-Acting Injectable CAB and RPV

Practical considerations regarding the feasibility of monthly IM administration of CAB and RPV deserve attention. Because the currently approved formulations are recommended to be administered only by a health care provider, the potential exists for strain on clinical systems, pharmacies, and patients. A 23-gauge, 1½-inch IM needle is recommended for the injection and is provided in the product packaging. However, longer, 2-inch needles should be used in patients with body mass index >30 kg/m^2. Ventrogluteal IM injections should be given on opposite sides when possible, or at least 2 cm apart if given on the same side. Individuals with buttock implants or fillers may not be appropriate candidates because of concerns regarding drug absorption. Care should be taken to administer only into gluteal muscle, preferably ventrogluteal.

OTTTIMIZZAZIONE