FEASIBILITY OF IMPLEMENTING LONG-ACTING INJECTABLE ANTI-RETROVIRAL THERAPY TO TREAT HIV: A SURVEY OF HEALTH PROVIDERS FROM THE 13 COUNTRIES PARTICIPATING IN THE ATLAS-2M TRIAL

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Abstract

Introduction: Long-acting (LA) injectable antiretroviral therapy (ART), with cabotegravir (CAB) and rilpivirine (RPV), was found to be non-inferior to daily oral ART in Phase 3 trials for efficacy, with high patient acceptability, tolerability and satisfaction. Limited information on provider experiences with LA ART exists, which is critical to inform real world implementation.

Methods: An online survey was sent to 449 health providers from the 13 countries participating in the Phase 3b ATLAS-2M trial of the administration of CAB LA + RPV LA every 8 weeks (Q8W) compared to every 4 weeks (Q4W). A total of 329 (73%) providers responded to the survey and 293 provided information on LA ART feasibility. Based on prior formative qualitative research, we developed composite scores of logistical barriers, clinical concerns and patient benefits related to LA ART. Multivariable regression was used to identify factors related to the feasibility of LA ART every month and two months in the context of routine care including the barriers, concerns and benefits scores, and geographic and provider variables.

Results: A majority of providers indicated that it would be very feasible (62.8%) or somewhat feasible (32.1%) to administer monthly LA ART in their clinics. Feasibility scores were higher for delivering LA ART every 2 months vs. every month (mean 28.3 vs. 26.9; p-value <0.001). In multivariable logistic regression, providers from Africa had significantly higher odds of perceived overall feasibility of monthly LA ART (aOR 2.9, 95% CI 1.9-4.4) compared to those from other regions, as did those reporting a greater number of LA ART patient benefits (aOR 1.1, 95% CI 1.0-1.1) compared to those reporting fewer benefits. Providers reporting a greater number of barriers to patients returning to clinic appointments had a significantly lower odds of perceived feasibility (aOR 0.8, 95% CI 0.7-1.0).

Conclusions: Clinical and operational guidelines, provider training, human and material resources, and patient support systems are needed to optimize LA ART implementation.

Background

- In response to challenges to daily oral ART adherence and patient preferences, LA ART is under study to treat HIV.
- CAB + RPV is one formulation of LA ART involving intramuscular injections delivered every 4 or every 8 weeks administered by trained health providers.
- Phase 3 trials found Q8W and Q4W CAB + RPV to be non-inferior to daily oral ART in terms of rates of viral suppression.
- Building on our prior qualitative work,[1] we developed a survey to assess the feasibility of LA ART among providers involved in the ATLAS-2M Phase 3 trial.

Methods

Procedures

- We conducted a cross-sectional survey of clinical care providers from ATLAS-2M to evaluate the feasibility of implementing LA ART outside of clinical trials.
- We developed composite scores to examine the role of perceived logistical barriers related to patients' adherence to clinic appointments, clinical management concerns and perceived patient benefits.
- The online anonymous survey was administered February to May 2019 using Qualtrics © and was sent to 449 eligible providers across the 13 countries participating in ATLAS-2M (Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden and the USA).

Participants

- Eligible providers had to have: 1) administered injections, 2) provided clinical oversight to patients during the trial, and/or 3) monitored and managed subject safety.
- A total of 329 of the 440 eligible providers initiated the survey (73% response rate) and 293 provided information on the feasibility of LA ART in their clinics.

Analysis

- We used multivariable regression to assess factors associated with the perceived feasibility of implementing LA ART, including logistic regression for binary outcomes and multinomial regression for categorical outcomes.
- Logistic models utilized generalized estimating equation (GEE) procedures to account for intraclass (country) correlation. For multinomial analyses we adjusted for clustering related to country by including country in the models.

Results

As seen in Table 1, survey respondents came from five geographic regions, more than half were physicians, most had experience with LA ART from prior clinical trials, and roughly half of participating providers had direct experience administering injections.

Table 1. Characteristics of Participating Clinical Care Providers (N=293)

Variable	N	%
Provider characteristics		
Region		
Europe	179	61.1
North America	68	23.2
Asia/Pacific	18	6.1
Africa	16	5.5
Latin America	12	4.1
Role in clinic		
Physician	172	58.7
Nurse/PA	72	24.6
Pharmacist	11	3.8
Research staff	38	13.0
Prior trial involvement		
1-2 clinical trials	155	52.9
3+ clinical trials	138	47.1
Injection experience		
Yes	121	43.1
No	160	56.9

- Our primary outcome was **overall feasibility** of implementing monthly LA ART:
  - *"Overall, how feasible would it be to facilitate administering monthly injections of CAB + RPV LA at your clinic?"*
  - This variable was dichotomized as: 1=very feasible, 0=somewhat/not very/not at all feasible.
    - **62.8% of providers** reported that monthly LA ART was **very feasible**
    - **37.2%** reported it was **somewhat/not very/not at all feasible**
- Secondary outcomes included composite measures of the feasibility of implementing Q4W compared with Q8W LA ART.
  - The **mean level of feasibility** was significantly higher for Q8W vs. Q4W (mean 28.3 vs. 26.9; p-value <0.001).
- **LA ART Feasibility score:** Providers indicated how feasible (4-point Likert scale: very feasible, somewhat feasible, not very feasible and not at all feasible) they consider Q4W and Q8W LA ART to implement in their clinics in terms of:

1. Space
2. Personnel
3. Clinic flow
4. Cold chain
5. Refrigeration
6. Stocking space
7. Maintaining stock
8. Logistics of patient follow-up

The scores were categorized as follows for the purpose of regression analyses:
Lo <= 24 Medium = 25-31 Hi = 32

Figure 1. Barriers to LA ART Appointment Adherence: Frequency by Region

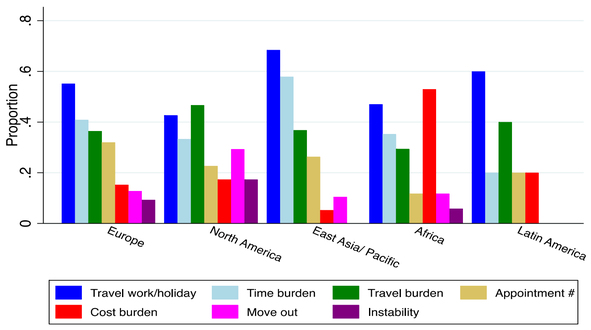

Figure 1 shows **logistical barriers** providers reported as impacting patient's adherence to clinical appointments to receive injections during trial:

- Almost 2/3 reported **travelling** (work or holiday), followed by almost half reporting **travel burden** (distance to clinic) and **time burden** (waiting times, appointment durations, etc.) as the top logistical barriers to clinic appointment adherence among patients.
- **Cost** was reported as a significant burden in **Africa**.

As shown in Figure 2, **privacy** was reported as a very important perceived patient benefit of LA ART in most regions (~70%). There were differences based on region regarding other benefits:

- **Lifestyle:** most important benefit in Europe (82%) & Latin America (100%)
- **Convenience:** most important benefit in North America; E. Asia, Africa (~90%)
- **Food security:** Not having to have to take food with pills most salient in Africa

Figure 2. Benefits of Injectable LA ART Regimen: Frequency by Region

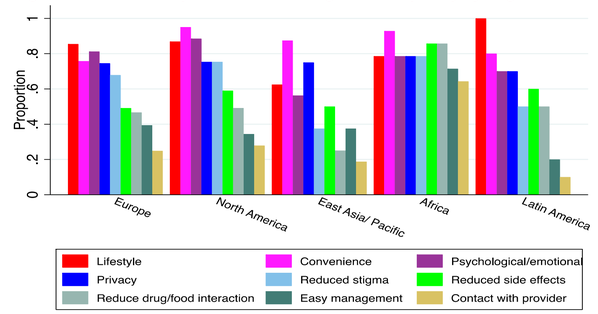

Table 2. Provider Clinical Concerns With LA ART (Very/Somewhat Concerned):

	N (293)	%
Patients not returning to clinic on time for injection appointments	224	79.7
Risk of resistance for patients not adherent to injections	195	69.4
Patients moving out of the area	182	64.8
Patients switching to a different provider	154	54.8
Drug interactions and comorbidities (e.g. TB, HCV)	138	49.1
Taking a patient off CAB LA + RPV LA and switching to oral ART	120	42.7
The oral lead-in phase before starting injections	68	24.2

Table 2 shows providers top concerns about patient management all focused on patients' adhering to injection schedules:

- **Patients not returning to the clinic on time** for injection appointments (80%).
- **Risk of resistance** due to non-adherence to injection schedule (69%).
- Fear of patients **moving out of area** was mentioned by more than half (65%).

Table 3. Multivariable Logistic Model of Providers Considering Monthly LA ART "Very Feasible" (N=266)

Variable	aOR	95% CI
Region: (ref: Europe)		
North America	1.4	0.79, 2.30
Latin America	0.7	0.22, 2.27
Asia/Pacific	1.4	0.73, 2.84
Africa	2.9***	1.87, 4.35
Role in clinic (ref: physician)		
Nurse/physician assistant	1.1	0.73, 1.55
Research staff/pharmacist	0.8	0.51, 1.29
Prior trial involvement (ref: 1-2 trials)		
3+ clinical trials	1.6	0.76, 3.32
Barriers, concerns and benefits scores (per unit change in score)		
Barriers score	0.8**	0.70, 0.94
Concerns score	1.0	0.95, 1.09
Benefits score	1.1**	1.03, 1.13

***=p<0.001; **=p<0.01; *=p<0.05

Table 3 shows geographic region, logistical barriers, adherence concerns and patient benefits were significantly associated with feasibility of monthly LA ART.

- **Regions:** Providers from Africa had an increased odds of reporting Q4W LA ART as "very feasible" (aOR 2.9; p<0.001) compared to European providers.
- **Benefits:** Providers reporting a greater number of benefits of LA ART had a significantly increased odds of overall feasibility of Q4W LA ART (aOR 1.1 per unit change in benefits score; p=0.003).
- **Barriers:** Providers reporting a greater number of barriers to LA ART had a significantly decreased odds of overall feasibility of Q4W LA ART (aOR 0.8 per unit change in barriers score; p=0.007).
- **Clinical concerns:** While trending towards a negative influence on Q4W LA ART feasibility, concerns did not remain significant in multivariate analysis.

Table 4. Multivariable Multinomial Model of Feasibility Scores for Q4W and Q8W LA ART (N=266)

	Feasibility of Q4W LA ART				Feasibility of Q8W LA ART			
	Medium vs low		Hi vs low		Medium vs low		Hi vs low	
Variable	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Region (ref: Europe)								
North America	2.6**	1.3, 5.2	2.1	0.9, 5.4	2.6***	1.5, 4.3	1.0	0.5, 1.7
Latin America	0.4*	0.2, 0.8	0.4	0.0, 4.0	0.1	0.0, 1.0	0.3***	0.2, 0.6
Asia/Pacific	0.6	0.3, 1.5	1.0	0.5, 2.0	0.3**	0.1, 0.6	0.4***	0.3, 0.7
Africa	0.8	0.5, 1.9	3.0*	1.2, 7.7	4.0***	2.5, 6.5	3.5***	1.9, 6.3
Role in clinic (ref: physician)								
Nurse/PA	0.8	0.4, 1.5	0.6	0.3, 1.0	0.5*	0.2, 0.9	0.5**	0.3, 0.8
Res. staff/phar.	0.7	0.3, 1.6	0.4	0.2, 1.0	0.3	0.1, 1.1	0.4*	0.2, 0.8
Prior trial involvement (ref: 1-2 trials)								
3+ clinical trials	0.5	0.3, 1.1	1.1	0.5, 2.3	0.6	0.2, 1.6	0.8	0.4, 1.6
Barriers, concerns and benefits scores (per unit change in score)								
Barriers score	0.9	0.8, 1.1	0.7**	0.6, 0.9	0.9	0.7, 1.0	0.8**	0.7, 0.9
Concerns score	0.9**	0.8, 1.0	1.0	0.9, 1.1	0.9	0.8, 1.0	0.9*	0.8, 1.0
Benefits score	1.1**	1.0, 1.1	1.2***	1.1, 1.3	1.0*	1.0, 1.0	1.2***	1.1, 1.3

***=p<0.001; **=p<0.01; *=p<0.05

Table 4 shows multivariable multinomial regression models for composite feasibility scores of Q4W and Q8W LA ART:

- **Region:** Both African and North American providers reported significantly greater odds of feasibility at Q4W and Q8W. East Asia/South Pacific and Latin America reported significantly lower feasibility of delivering LA ART.
- **Logistical barriers** with adherence to clinic appointments were significantly associated with LA ART feasibility at Q4W and Q8W, as were concerns related to initiating patients on LA ART.
- Perceived **patient benefits** related to LA ART were significantly associated with feasibility at both Q4W and Q8W.

Conclusions

- Results suggest feasibility of successfully implementing LA ART in clinical practice is relatively high based on reports of providers participating in LA ART trials.
- Logistical barriers and clinical concerns remain salient including: concerns related to the patient's ability to adhere to clinic appointment schedules to receive injections, and clinical management concerns.
- Despite potential challenges, provider perceptions of important patient benefits of LA ART were significantly associated with a greater likelihood of perceived feasibility, indicating that providers are motivated and responsive to both the clinical needs and psychosocial preferences and well-being of patients.
- Significant variation in perceived feasibility of LA ART implementation by geographic region observed suggests that strategies to introduce LA ART into routine care must be tailored to the needs of a given geographic and clinic setting.

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Reference: 1. Kerrigan et al. *PLoS One*. 2018;13:e0190487.

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