



Long acting ARV HIV treatment regimens: Key Considerations for Stakeholders

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Vision: Healthy Communities, Healthy People



Introduction

- Welcome and Introduction of Speakers
- Review of Agenda
 - Disclosures
 - Background
 - Potential Impact of long-acting (LA) antiretrovirals (ARVs)
 - Potential Impact on RWHAP and ADAP
 - Q&A and Discussion



Disclosures

LCDR Emeka Egwim, PharmD, RPh has no relevant financial or non-financial interests to disclose.

Glenn Clark, MSW has no relevant financial or non-financial interests to disclose

Tim Horn, MS receives grant/research support from: AbbVie, Gilead Sciences, Janssen, and ViiV Healthcare

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Learning Objectives

1. Describe the pharmacology of the LA ARV
2. Understand the findings from the LA ARV clinical trials
3. Discuss implementation approaches for providers, patients, and payers

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Health Resources and Services Administration (HRSA)

Overview

- Supports more than 90 programs that provide health care to people who are geographically isolated, economically or medically vulnerable through grants and cooperative agreements to more than 3,000 awardees, including community and faith-based organizations, colleges and universities, hospitals, state, local, and tribal governments, and private entities
- Every year, HRSA programs serve tens of millions of people, including people with HIV/AIDS, pregnant women, mothers and their families, and those otherwise unable to access quality health care



HRSA's HIV/AIDS Bureau (HAB) Vision and Mission

Vision

Optimal HIV/AIDS care and treatment for all.

Mission

Provide leadership and resources to assure access to and retention in high quality, integrated care, and treatment services for vulnerable people with HIV/AIDS and their families.



HRSA's Ryan White HIV/AIDS Program

- Provides comprehensive system of HIV primary medical care, medications, and essential support services for low-income people with HIV
 - More than half of people with diagnosed HIV in the United States – nearly 519,000 people – receive care through the Ryan White HIV/AIDS Program (RWHAP)
 - Funds grants to states, cities/counties, and local community based organizations
 - Recipients determine service delivery and funding priorities based on local needs and planning process
- Payor of last resort statutory provision: RWHAP funds may not be used for services if another state or federal payer is available
- 87.1% of Ryan White HIV/AIDS Program clients were virally suppressed in 2018, exceeding national average of 62.7%



Source: HRSA. Ryan White HIV/AIDS Program Annual Client-Level Data Report 2018; CDC. HIV Surveillance Supplemental Report 2018;21(No. 4)



BACKGROUND

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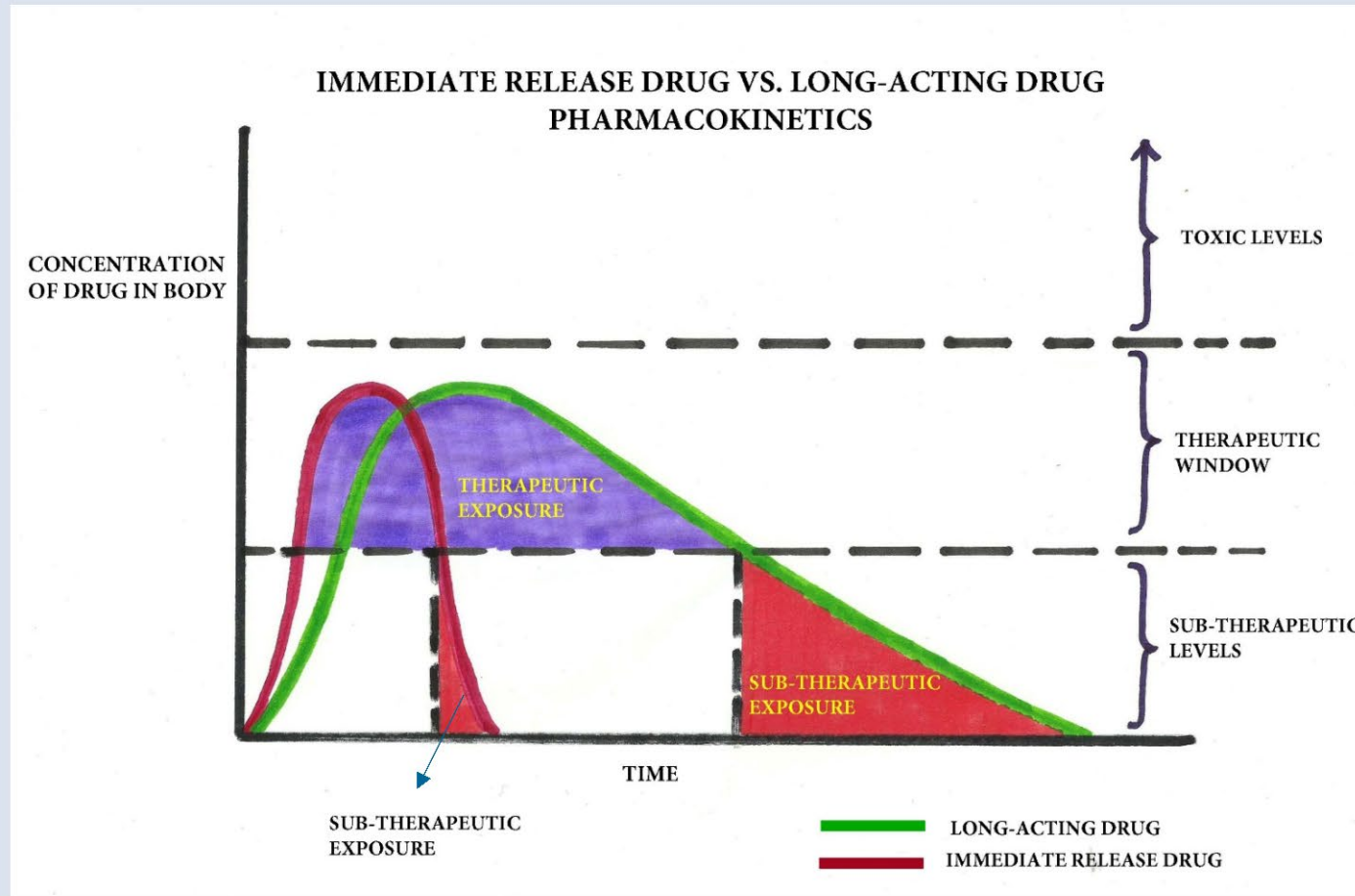
What is a Long-Acting Medication?

Drug formulation engineered to achieve the following over an extended period of time:

- Maintain therapeutic and efficacious levels
- Be slowly absorbed relative to the dose
- Persist in the tissues before being metabolized or excreted

Longer half-life compared to immediate, or delayed release formulations.

Immediate Release vs. Long-Acting Drugs



Potential Advantages of LA ARVs

- Address suboptimal adherence
- Ameliorate challenges associated with oral medications, including gastrointestinal, neurologic, or psychiatric disease
- Less frequent dosing & avoidance of pill fatigue
- Protection of health privacy
- Avoidance of HIV-related stigma

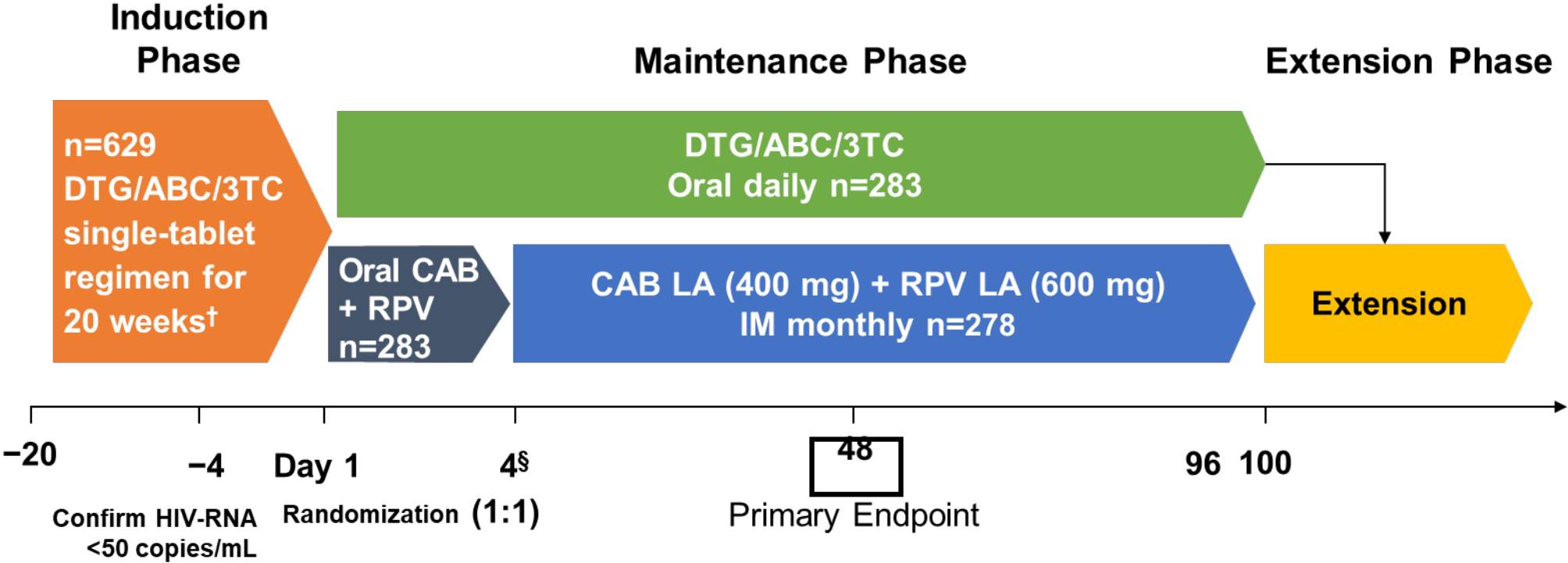
Long-Acting ARV Pipeline

ARV Class	Agent	Formulation	Development Stage
NRTI	Islatravir	Implant	Preclinical
	TAF	Implant and Injectable	Preclinical
	GS-9131	Implant	Preclinical
NNRTI	Rilpivirine	Injectable, Implant, Topical	NDA (Injectable) & Preclinical (implant, topical)
	Doravirine	Vaginal ring	EMA/WHO review
	Elsulfivarine	Injectable	Preclinical
INSTI	Cabotegravir	Injectable	Phase III/NDA, Phase II/III (Prevention)
	Raltegravir	Injectable	Preclinical
Entry Inhibitors	Ibalizumab	Intravenous	FDA Approved (Tx)
	PRO 140	Intravenous and Injectable	Phase III
	bNAbs (e.g., VRC01)	Intravenous	Phase II/III
	Combinectin	Intravenous	Preclinical
Capsid Inhibitors	GS-CA1	Injectable	Preclinical

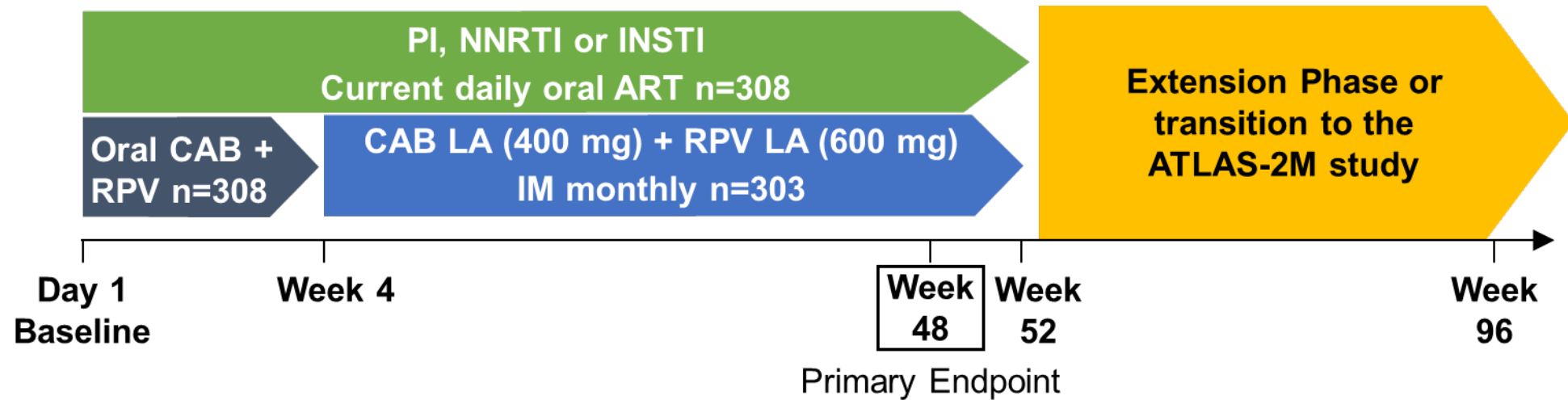
Long-Acting Cabotegravir/Rilpivirine (CAB/RPV)

- **Cabotegravir:** Strand-transfer integrase inhibitor being developed for HIV treatment and prevention; analog of dolutegravir
- **Rilpivirine:** Non-nucleoside reverse transcriptase inhibitor; first approved May 2011
- Formulated as a long-acting injectable nanosuspensions for intramuscular (IM) administration
- Also formulated/available as an immediate-release oral tablets for daily administration
- Possible FDA approval: Q1 2021

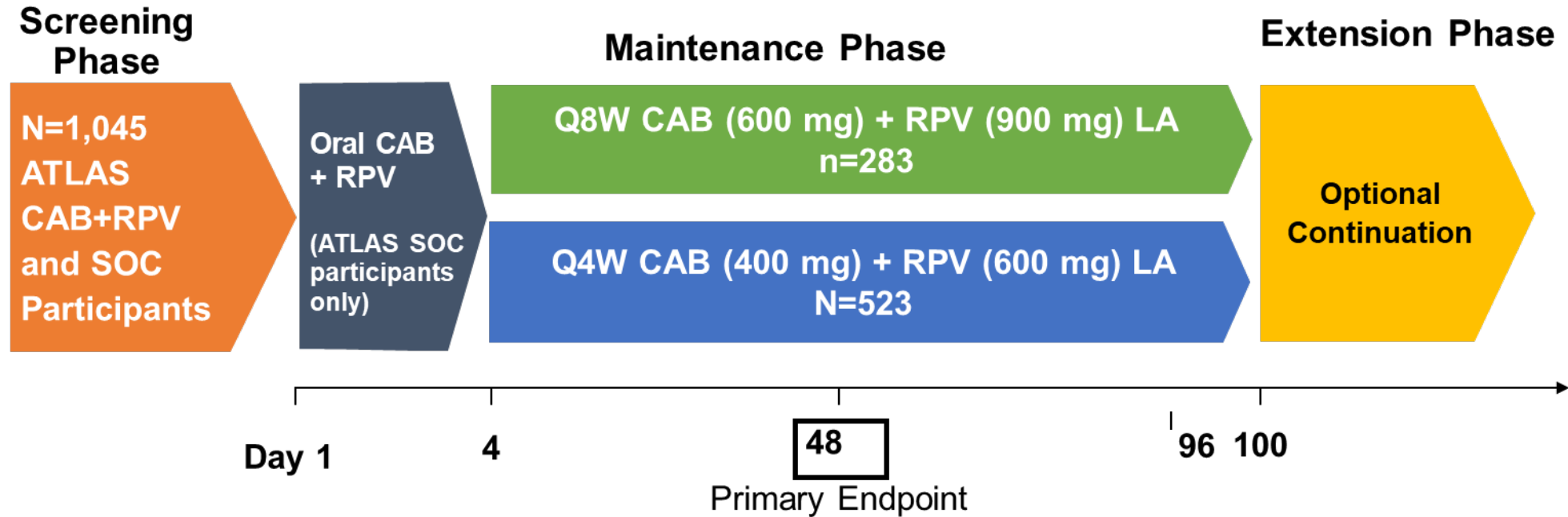
Phase III FLAIR Study



Phase III ATLAS Study

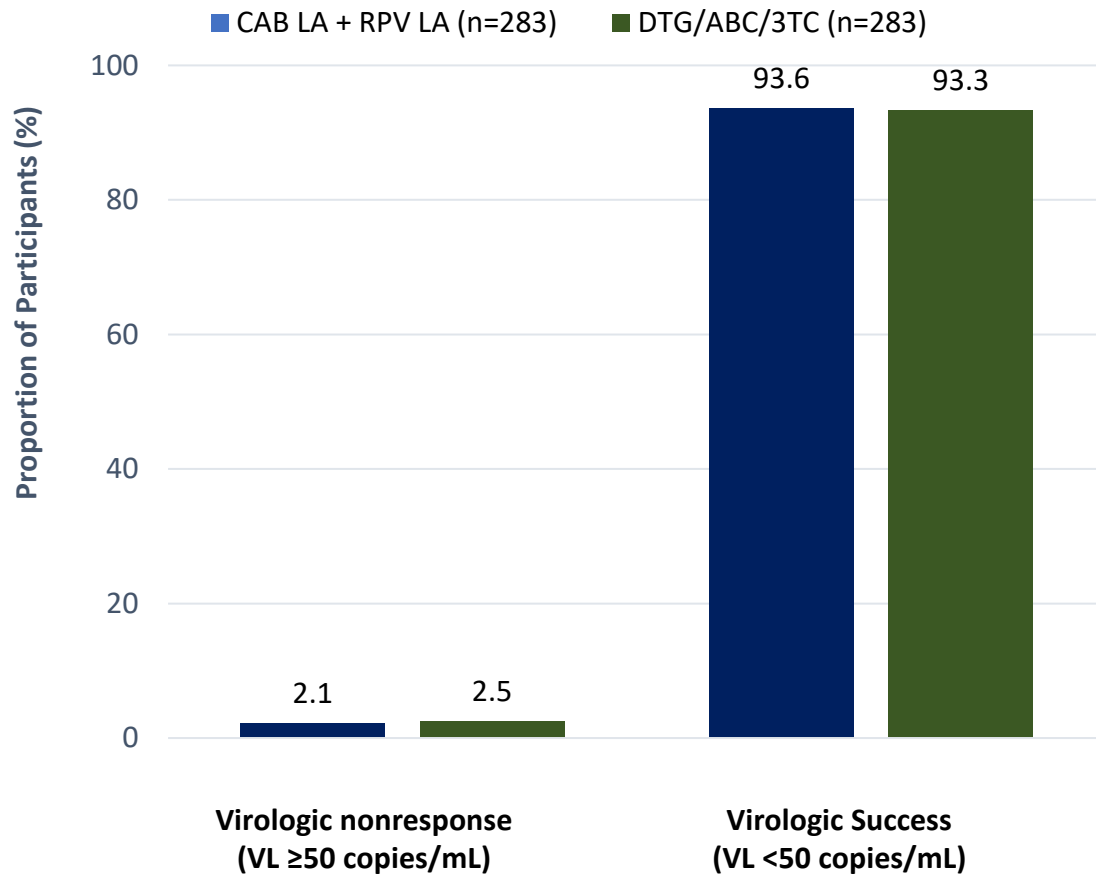


Phase III ATLAS-2M Study

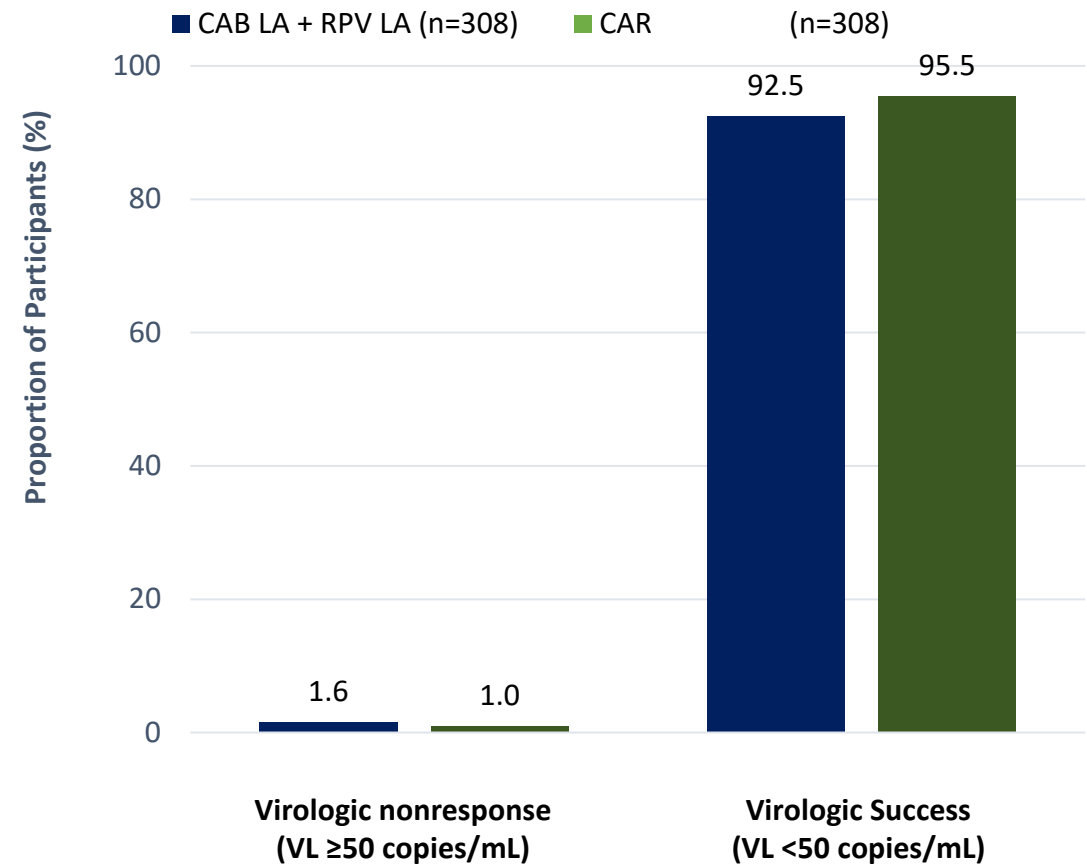


FLAIR & ATLAS: Noninferiority Achieved

FLAIR Virologic Outcomes

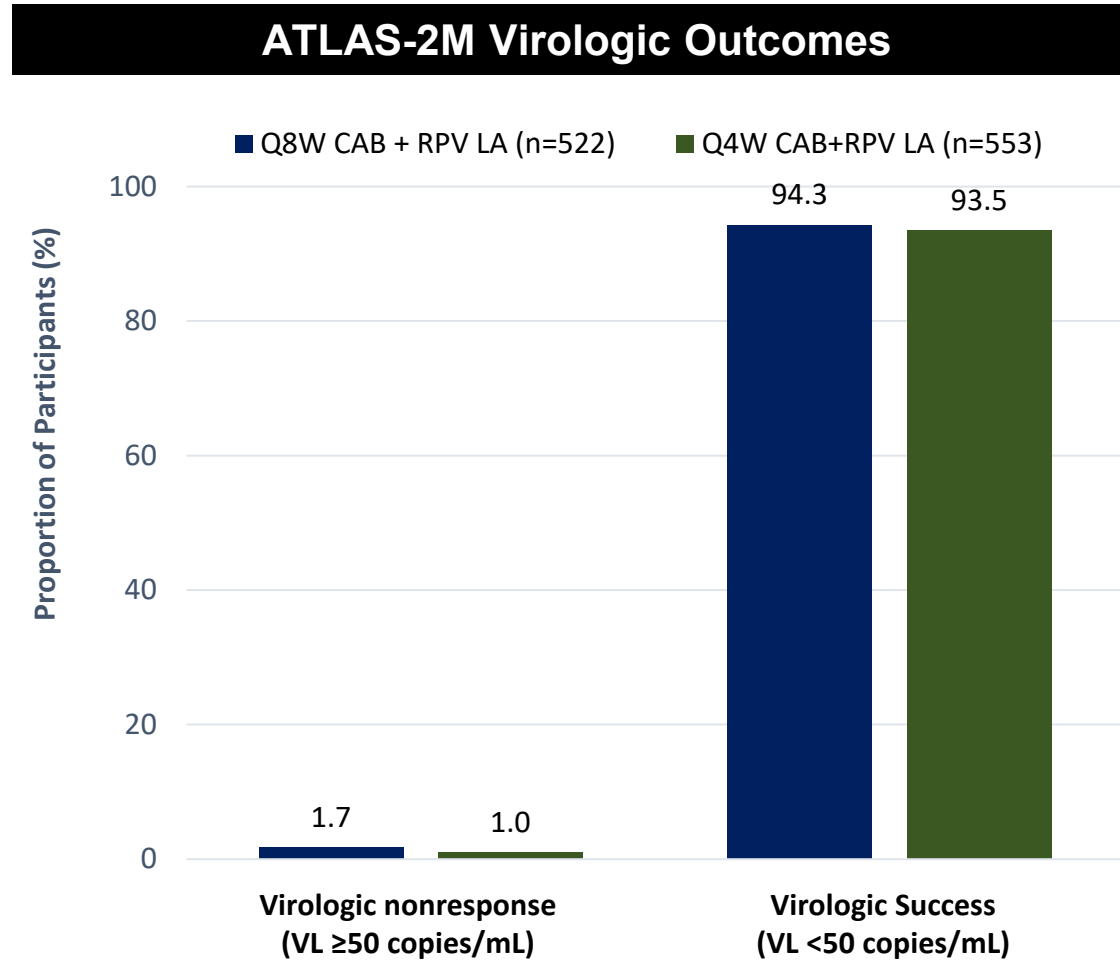


ATLAS Virologic Outcomes



Orkin C, et al. N Engl J Med. 2020;382:1124-35
Swindells S, et al. N Engl J Med. 2020;382:1112-23

ATLAS-2M: Noninferiority Achieved



Overton, et al. CROI 2020 (Abstract 34)

FLAIR & ATLAS Injection Site Reactions

	FLAIR CAB+RPV (LA) N=283	ATLAS CAB+RPV (LA) N=308
Participants receiving injections	278	303
Injections given	7,708	6,978
ISR events	2,203 (28.6)	1,460 (20.9)
Pain	1,879 (85.3)	1,208 (82.7)
Nodule	86 (3.9)	54 (3.7)
Induration	82 (3.7)	54 (3.7)
Swelling	38 (1.7)	48 (3.3)
Warmth	38 (1.7)	NR
Grade 3 ISR pain	12 (<1)	20 (1.7)
Median duration of ISRs, days	3	3
Participant with ISR leading to withdrawal	2 (<1)	4 (1.3)

FLAIR and ATLAS Participant Satisfaction

"They like not having to worry about taking their pills every day...they get their injection and they're good to go. They don't have to think about having HIV every day, they don't have to worry about co-workers or housemates seeing their pill bottles – there's maybe some relief of the stigma of HIV if they don't have to think about it every day."

– Dr. Susan Swindells,
University of Nebraska,
ATLAS Investigator

- FLAIR: 99% preferred the LA regimen over induction phase treatment
- ATLAS: 97% preferred LA regimen over previous oral therapy
- ATLAS-2M:
 - 98% without prior Q4W experience preferred Q8W LA regimen over previous oral therapy
 - 94% with prior Q4W experience preferred Q8W LA regimen; 3% preferred Q4W LA regimen

CAB/RPV LA Dosing Considerations

- **Initial therapy:** Standard ART regimen to achieve/maintain virologic suppression
- **Oral lead-in dosing:** 30 mg cabotegravir plus 25 mg rilpivirine once daily for four weeks
 - Limited distribution system anticipated
- **IM loading dose:** Two 3 mL IM injections (600 mg cabotegravir plus 900 mg rilpivirine) administered once
- **IM maintenance dosing:** Two 2 mL IM injections (400 mg cabotegravir plus 600 mg rilpivirine) administered four weeks after the IM loading dose and every four weeks thereafter (+/- 1 week)
- Provider administered gluteus medius injections; z-tracking technique
- Standard oral regimen to cover CAB/RPV LA injection delays

Specialty Distribution

- CAB/RPV LA will primarily be available from several specialty pharmacies (SP) and specialty distributors (SD) with experience in handling, dispensing, and shipping provider-administered drugs and biologics
- Specialty distributors are often divisions of the “Big Three” full-line wholesalers
 - Product ordering via AmerisourceBergen, McKesson, and Cardinal Health anticipated
- Product ordering via specialty pharmacy in ADAP’s PBM network also feasible; contracting may be required



Cold-chain transport and storage

Provider Administration

- ViiV Healthcare primarily focused on clinic and office administration
- Clients living with HIV usually seen every three to six months
- Capacity and staffing to support monthly injections – scheduling, exam rooms, wait times, MD/PA/NP/RN availability, drug product storage and inventory management
- Capacity and staffing to support monthly retention; client reminders and diligent missed-appointment follow up
- RWHAP provider network sufficiency to meet monthly administration needs of clients where they are
- Pharmacy administration: state law/policy dependent; capacity/space, expertise, cultural competence

Potential Impact of Long Acting ARVs on Payers

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Impact of Long-Acting HIV ARVs on Third-Party Payers

- Partly driven by **cabotegravir pharmacokinetics**
 - After a single dose, it persists in the body for up to:
 - 3 years in women
 - 1.5 years in men
 - Is characterized by a sub-therapeutic “long tail.”
- Also driven by its **approved uses**

Impact on Third-Party Payers - Continued

- Considerations include:
 - **Potential drug interactions**
 - Drug-drug
 - Drug-disease
 - **Risk and cost of resistance in cases of non-adherence**
 - Resistance to cabotegravir for individuals
 - Risk of transmitting resistant strains
 - Impact on efficacy of Integrase Inhibitors drug class?
 - Resistance to rilpivirine + cabotegravir combination therapy
 - **Potential effect on reproductive health**

Drug Pricing – Cost Considerations

- Price of long-acting vs. oral regimens
- Cost, per patient, per year
- Similar analysis of single tablet regimens (STR) vs. multi-tablet regimens (MTR).
- Express Scripts Nov 2018 Report:
“When looking at differences in adherence and cost between MTRs and STRs, our research suggests single-tablet regimens are associated with better adherence and lower costs compared to multi-tablet regimens.”



Drug Pricing – Drug Administration Logistics

- Monthly administration by professional vs. self administered oral regimen
- White Bagging vs. Brown Bagging vs. Buy & Bill
- Drug delivery costs
- Professional service fees (Pharmacist dispensing fee vs. provider administration fee)

Costs	White Bagging	Brown Bagging	Buy & Bill
Drug Ingredient	✓	✓	✓
Pharmacist Professional Dispensing	✓	✓	✗
Provider Drug Administration	✓	✓	✓
Drug Delivery	✓	✗	✗
Missed Fills (Abandoned Doses)	✓	✓	✗



CAB/RPV LA: Medical vs. Pharmacy Benefit

- **Medical Benefit**
 - CMS decision: medical vs. pharmacy benefit; medical benefit determination anticipated
 - Buy-and-bill; product and administration cost sharing
 - White bagging; administration cost sharing
 - Pharmacy bills for drug cost and charges drug cost sharing
 - Provider bills for administration and other associated office visit costs and charges medical cost sharing
- **Pharmacy Benefit**
 - White bagging; administration cost sharing



Clinical Considerations

- Indication requires success with lead-in oral regimen
- Drug Utilization Review Boards
- Pharmacy & Therapeutics Committees
 - Implementation of utilization management techniques:
 - Prior authorization / Step therapy / Clinical Criteria
- Cost and public health impact of:
 - Preventing resistance due to long tail and non-adherence
 - Resistance occurring
 - Losing efficacy of specific drug as a treatment tool
 - Losing efficacy of drug class
 - Addressing spread/outbreaks of resistant strains



Primary Payer Considerations: Medicaid

- As of 2018 at least 31 percent of RWHAP clients were Medicaid beneficiaries
- Another 7.9 percent dually eligible for Medicaid and Medicare
- Provision at Section 1927(d)(4)(C) of the Social Security Act
- With regard to establishing a Medicaid formulary:
 - “a ... drug may only be excluded with respect to the treatment of a specific disease or condition for an identified population if, based on the drug’s labeling, ... the excluded drug does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome of such treatment for such population over other drugs included in the formulary ...”*
- “Pay more to solve a clinical issue that’s already been addressed?”



Primary Payer Considerations: Medicare

- **Medicare**
 - Provider-administered drug/buy-and-bill: Medicare Part B
 - Cost sharing: Up to 20% of Medicare allowable cost (Average Sales Price + 6%); possibility of separate 20% cost sharing on administration/office visit charge
 - May be Part D pharmacy benefit/white bagging (e.g., MA-PD plans)
 - Cost sharing: copayment or coinsurance on drug product; separate cost sharing for administration/office visit

Primary Payer Considerations: Commercial Insurance

- CAB/RPV LA more likely to be medical benefit; may not appear on drug formulary, but expected to be covered by most plans
- Medical benefit/buy-and-bill
 - Cost sharing: One or two cost-sharing payments may be required. Example: Only one if administered by nurse; two if administered by doctor or as part of an evaluation and management (E/M) visit. Coinsurance (% of list price) anticipated.
- Pharmacy benefit/white bagging
 - Cost sharing: Two cost-sharing payments generally required. Example: One to specialty pharmacy, one to provider for office visit/administration



Primary Payer Considerations: ADAPs/Buy-and-Bill

- **Buy-and-bill**
 - Provider maintains stock of CAB/RPV LA purchased at list price from specialty distributor; submits bundled claim (product + administration) to Part B or ADAP; paid by ADAP and/or Part B; ADAP submits rebate claim to manufacturer
 - ADAP may need to establish reimbursement rate with provider (e.g., Average Sales Price + 6%); contracting with providers may apply

Primary Payer Considerations: ADAPs/White Bagging

- **White bagging (Rebate model):**
 - Provider orders refill from wholesaler or SD; ADAP invoiced and pays list price of drug; paid product shipped to provider; provider submits separate medical/administration claim to ADAP or Part B; ADAP submits full rebate claim to manufacturer

Primary Payer Considerations: ADAPs/White Bagging, continued

- **White bagging (Direct purchase models):**
 - Provider orders refill from ADAP; ADAP orders from wholesaler or SD, pays ACTF-negotiated net price of drug; product shipped to provider; provider submits separate medical/administration claim to ADAP or Part B
 - Provider orders refill from wholesaler or SD; product shipped by SD to provider; SD stock replenished via ship-to/bill-to mechanism; provider submits separate medical/administration claim to ADAP or Part B



Potential Impact of LA ARVs on RWHAP and ADAP

Glenn Clark, MSW
ADAP Advisor,
DSHAP, HAB



Impact on RWHAP providers and ADAPs/Applicability

- Applicability
 - While this is a wonderful advance in treatment, the current guidelines for this initial LA ARV would not support its use with a number of the populations for whom we face challenges in helping them reach viral suppression.
 - The challenge is *getting* clients to an undetectable viral load, not necessarily in *maintaining* an undetectable viral load.

Impact on RWHAP providers and ADAPs/Uninsured

- Increased costs for uninsured patients
 - Costs of increased number of clinic visits (monthly visits versus every three to six months), including staffing.
 - Potential increased costs of medication
 - Increased costs for drug product storage and inventory management
 - Potential increased costs to support monthly retention; client reminders and diligent missed-appointment follow up

Impact on RWHAP providers and ADAPs/Insured

- Increased systems and coordination challenges for insured clients
 - Capacity and staffing to support monthly injections – scheduling, exam rooms, wait times, MD/PA/NP/RN availability, drug product storage and inventory management
 - Capacity and staffing to support monthly retention; client reminders and diligent missed-appointment follow up

Impact on ADAPs Specifically

- For ADAPs
 - Potential increased costs of medication (especially if Medicaid and 3rd party payers don't cover the medications).
 - Challenges with engaging with specialty pharmacies and specialty distributors/ coordinating provider-administered medication
 - Challenge with setting up systems to pay for administering the medications

HAB Guidance for ADAPs re: LA ARVs

- On December 4, 2019, HAB released a letter from Dr. Laura Cheever
 - The letter states that it is allowable for ADAP to pay for the cost of administering an antiretroviral medication on the RWHAP ADAP formulary, including the cost of an office visit exclusively for medication administration
 - For clients with health care coverage, ADAPs can cover the client's cost-sharing related to that visit.
 - The letter states that HRSA recommends ADAPs consider adding long-acting ARVs to their formularies, once available.



Preparing for LA ARVs: Projecting Impact

- Work on methodology for projecting the potential increase in costs to the RWHAP provider and ADAP for clients who are prescribed LA ARVs
 - Uninsured clients
 - Insured clients

Preparing for LA ARVs: Acquisition & Payment

- Explore what changes your system will require to acquire and pay for the LA ARV and its administration
 - Will this require new contracts? If so, what process and timeline is needed to execute?
 - Regardless of whether a new contract is required, are new partnerships/relationships needed?
 - What coordination will be needed between the ADAPs and other RWHAP providers to facilitate use of LA ARVs?
 - For ADAPs, if they choose to pay for the cost of administering the medications, what mechanism will they use to accomplish this?



Preparing for LA ARVs: System Capacity

- Explore what changes will be needed in your system to handle the additional clinic appointments and monitoring
 - What process and timeline are needed to accomplish these changes?

Q&A

Questions?



Discussion

Discussion



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