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"The clinician's perspective"

"I feel a mounting sense of anxiety about how much work there is to do to get [LAI ARVs] into the people who [need them]"

Mass treatment in the early 2000s

We had an imperfect drug, but we made it work.

- d4T (AZT) + 3TC + EFV or NVP. 3 tablets am and 2 tablets pm.
- Various forms of rationing. Balancing toxicity vs cost vs level of immunosuppression (CD4); Based on adherence visits or systems barriers.
- We started building the delivery system as we went.

Takeaways.

- We had drug to test the system.
- Many of the things we feared never happened. Mass resistance never became a programmatic issue – It informed the next round of drugs.

Cycle of ARV introduction in the LA era

A new product must offer a big step forward.

- **LAIs offer a huge advancement in terms of dosing.**

Then, negotiations:

- Price. Is it reasonable to replace what we currently have?
- Co-formulations in the first line. **This falls aways with the current LAIs.**

Specific considerations are different than in the past.

- TB drug interaction should not be a barrier for first-line therapies.
  - ◊ TB affects <1% PLWH at ARV initiation, and incidence falls on ART, even without IPT.
  - ◊ EFV- and DTG-based regimens work perfectly well for the few months ATT is needed.
- HBV coverage should not be required to advance a LA product.
  - ◊ Moving into the LA era, we will need to discuss what to do when HIV therapies stop covering HBV (i.e., No ramivudine- or TFV-based regimens in the mix).
- **Pregnancy and breastfeeding becomes central.**
  - ◊ Due to the sheer number of women who are vulnerable to infection and are presenting with new or re-infection.
  - ◊ The litmus test for new regimens should be if they can be used among women of child-bearing potential (LEN, CAB, and TLD have an evidence base; ISL and other drugs do not).
- Alignment with children and adolescents is desirable.
- Aging and comorbidities are increasingly important
  - ◊ Diabetes mellitus and frailty (i.e., Not the classic HIV co-morbidities).
- Resistance warrants engagement but is a less pressing issue.

Then, the dance around what should happen first.

- Guideline vs recommendation vs generic uptake vs adoption.
  - ◊ Generics will not manufacture a formulation before it is in the guidelines; Then need a volume guarantee, and finally (hopefully) something useful happens.
    - * That is what happened with TLD; TLD now completely dominates the guidelines in LMICs.

Challenges for health systems

LA HIV treatment.

- All current LAIs require HCW administration. Extra tablets for bridging and/or loading add complexity.
- Choice means more than one regimen. Supply lines; HCW prejudice; Switching.
- Reminders, tails, and loss to follow up. Once PEPFAR hands over a program, health systems (LMICs and high-income settings) are not good at getting people back for clinic visits.

LA HIV PrEP.

- LAI PrEP is completely unavailable (No CAB-LA or LEN in the system).
  - ◊ Studies show near 100% efficacy, but no lives have been changed.
- We are not moving quickly enough.
  - ◊ South Africa (SA) is touted as a PrEP success story, but it is a disaster.
    - * 10-20M people are eligible for PrEP.
    - * Product registrations: Oral TDF/xTC (2015); CAB-LA (2022); DPV ring (2022).
    - * 1.3M on PrEP (~ 50% re-starts); Only 1685 on CAB-LA and 790 on DPV ring (AVAC data as of 9/24).
  - ◊ ***CAB-LA has been licensed in SA for over 2y but is not available for purchase.***

Plan for LAI HIV PrEP

CAB-LA.

- Cannot be purchased from ViiV for treatment, prevention, or research. Very few, highly regulated implementation projects via donated CAB.
- Small volumes will trickle into the market via three generics at a unknown price in 2027. More than 7y after efficacy shown.

LEN

- Gilead access statement is totally vague beyond a willingness to work with communities to make LEN available.
- Volume, price point, and plan are unknown. ***Doses for 100M are needed.***

What does this mean?

- LAI PrEP programs cannot be scaled when pharma is gate keeping the two drugs we need.
  - ◊ It is impossible to test CAB-LA at scale with current volumes, even for key populations.
    - * The largest study in South Africa has 2000 participants.
  - ◊ Endless meetings on roll-out of a drug that is unavailable are just wishful thinking.
- Governments will not engage with buying LAIs until a price is set.

Plan for LAI HIV treatment

Context.

- Most people on ARVs want LAIs (not only key populations).
- Very few people initiating ARVs are truly ART-naive (<10%).

LAI CAB/RPV.

- The products are registered with no access from ViiV or Janssen.
  - ◊ The immediate compelling indication is non-adherent populations – We need it yesterday.
    - * The only way to access these life-saving products would be via some compounding mechanism.
  - ◊ Significant challenges: Cold chain; Resistance; Administration; and Cost.
    - * Not likely to replace TLD because the cost of the combination alone is so high.
- There are no other options.
  - ◊ Weekly oral LEN/ISL are the only other products on the horizon (Promising P2 data).
  - ◊ There is total gate keeping by pharma on other obvious combinations (e.g., CAB/LEN).
  - ◊ Each pharmaceutical company has its own issue regarding access.
    - * Janssen has given no indication of a RPV access plan.
    - * Gilead (LEN) will hopefully do the right thing.
    - * ViiV (CAB) has been chaotic from the start.
    - * Merck (ISL) has a pipeline but has not been engaged in terms of access.

What does this mean?

- It will likely be >10y before widespread access to LAI treatment.
  - ◊ Even if all companies granted instant access, more studies are needed to persuade WHO, guidelines committees, and governments on use of novel LAI combinations.
    - * Different drug combinations; Switch studies; PK; Naive, unsuppressed, and special population studies.
    - * ADVANCE took 4-5y to get the first results.
  - ◊ Then, we need to work on how to scale it.
- Harmonization of efforts is missing.
  - ◊ TLD introduction was the final success of the OPTIMIZE consortium.
    - * Convened people from every sector; Many parallel projects were conducted (Optimization, Patents, PK studies, Guidelines, etc); and Many projects fell by the wayside.
  - ◊ LEAP is trying to do the right thing on the front end but needs the next steps to get LAI ARVs where they are needed.