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Focus Group 4 – The future of bNAbs for HIV treatment and prevention
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Discussion questions.

- Is a companion assay necessary to identify suitable candidates for treatment with bNAbs?
- How susceptible does the virus need to be?
- If a single bNAb is used as PrEP, what proportion of viruses in a region should be susceptible to support implementation?
- What is the ideal dosing schedule for a bNAb regimen to be used as LA ART
- What is the ideal dose and dosing schedule for bNAbs to be used as PrEP?
- Is IV administration of bNAbs acceptable for treatment and prevention?

TPP drafted for the use of bNAbs for HIV in 2016.
Recommendations for HIV prevention.

- Product/efficacy profile.
  - Product: Two mAbs; prevent infection by >98% of strains.
  - Target population: adolescents/adults at high risk and infants of mothers with HIV.
  - Dose: 5mg/kg for adolescents/adults; 20mg/kg for infants
- Convenient dosing.
  - Q3M to Q6M for adolescents/adults; one-time dose at delivery for infants.
  - SC administration.
- Safe and tolerable: Rare AEs.
- Affordable: Cost of goods <$50 per person per year.

Recommendations for HIV treatment.

- Potent and durable suppression of HIV replication.
  - bNAb/regimen covers 95-98% of strains at target plasma concentration.
  - Dose <30mg/kg, ideally <1mg/kg.
  - No susceptibility testing needed; maintains viral suppression >48weeks; and infrequent emergence of resistant virus.
- Convenient dosing.
  - ≤Q1M; target is Q6M.
  - Home (SC) or infusion center (IV) administration.
  - A single needle stick is preferred (coformulation>coadministration>sequential administration).
- Safe.
  - Low risk of anaphylaxis or immune complex disease.
  - Rare SAEs with no increase in chronic inflammation markers or immune activation.
- Affordable: Cost of goods ≤ current first-line therapy.

Is a companion assay necessary to identify suitable candidates for treatment with bNAbs?
Factors to consider.

- Which bNAbs are being used, the HIV sub-type, and the assay design.

- ***The currently approved assay does not accurately predict bNAb susceptibility in VS patients.***

Improved bNAb susceptibility assays may be forthcoming.

- DAIDs initiative awarded four grants for the development of innovative assays (RFA-A1-22-022; R61/33).
- R61/33 mechanism: 3 years of funding for assay development and an additional 2 years of support with built-in measures for commercialization, *including regulatory compliance*.

Any requirement for testing before clinical care impacts clinical management.

- Introduces waiting time for assay results, additional costs, and other factors (e.g., Trophile assay for Maraviroc use).

Using multiple bNAbs might alleviate the need for susceptibility testing.

- A regimen comprising 3 to 5 bNAbs with broad coverage.

How susceptible does the virus need to be to the bNAbs in the regimen?

Considered two clinical scenarios.

- Replace small molecule ARV therapy with a combination of bNAbs as the sole regimen.
  - Failure on a purely bNAb regimen has minimal patient impact – small molecule ARV therapy remains an option.
- A hybrid combination regimen comprising 1 to 2 bNAbs and small molecule ARVs.
  - A higher threshold for bNAb susceptibility may be necessary, especially if the small molecule ARV has a low barrier to resistance (e.g., LEN).

Role of cell-to-cell transmission.

- Small molecule ARVs may target this mode more efficiently than bNAbs.
- Could lead to bNAb escape.

What proportion of viruses in a region should be susceptible to support implementation of bNAbs for PrEP?

bNAb product considerations.

- It was suggested that 2 to 3 bNAbs are needed to provide adequate coverage for protection.
- Combination agents should have a similar T½.
- The bNAbs should protect against 90% of circulating strains – a lower target than the 2016 TPP.

An important trait of bNAbs is no cross-resistance with small molecule ARVs.

- Using bNAbs for prevention preserves the option of using TLD for treatment, if needed.
- When using CAB-LA for prevention, there is a risk of acquiring INSTI-resistance and potentially compromising a class of drugs for treatment (i.e., TLD could not be used).

Why would an individual select bNAbs over oral PrEP, which has higher efficacy?

- Highlighted the distinction between efficacy, *optimal performance* of the regimen (FTC/TDF >90%), and effectiveness, *real-world performance* (FTC/TDF <90%).
- LA PrEP improves effectiveness by improving adherence.

Need to consider the public health approach vs individual patient care.

- What prevention product is most implementable on a global scale?

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- How can we protect the greatest number of individuals, most efficiently, and at the lowest cost?

What is the ideal dose and dosing schedule for bNAbs as LA ART and PrEP – is there a maximum dose and minimum dosing interval?

HIV treatment.

- Dosing should be compatible with SC administration to allow home administration.
  - Many monoclonal antibody therapies for other disease states are being developed for SC administration.
  - SC dosing: 2-10mg/mL with an injection volume limited to 2-3 mL.
  - A 1-gram dose would pose major volume challenges for the SC route.
- There is a clear need for LA strategies.
  - Over the same ten-year period, over 6 million individuals used oral PrEP, and there were 18 million new infections: Many stop taking oral PrEP after 6 months.
  - Side effects of bNAbs appear no different than placebo.
- Developing a new TPP that includes three categories: minimally effective; most commercially viable; and optimal characterstics.
- Generic LA ARVs will not be available in RLS for many years. It is very possible that bNAbs may be available sooner.

HIV prevention.

- What is the target bNAb concentration and corresponding dose (mg/kg)?
  - For ARV development, we have a sense of how high the concentration should be relative to the protein adjusted IC90.
  - The AMP trial provides a target: trough concentration of 10µg/mL with potential to go down to 1µg/mL.
- Is there a maximum amount that can be administered SC?
  - There are strategies that can expand the injection volume for SC dosing.
  - HVTN 140/HPTN 101 is exploring 40mg/kg administered via IV infusion vs multiple SC injections.
- Is there concern about the development of anti-drug antibodies?
  - Have not seen much with bNAbs, but the risk may be higher with SC vs IV dosing.
- Does the potency of circulating bNAbs decrease over time?

Is IV administration of bNAbs acceptable for HIV treatment and prevention?

3 bNAbs can be administered via one 10-minute IV infusion vs 9 SC injections.

- The IV route is practical. People can go to “non-healthcare settings” (more discrete option) or clinics.
- The SC injection has reduced bioavailability. Up to 35% of the dose is not absorbed.

The AMP trial demonstrates high adherence with IV infusions.

- Over 40,000 infusions have been administered in sub-Saharan Africa.

Age is a factor in determining pediatric utility.

- The IV route is not useful in neonates, but this may change as children get older.
- The SC route is important in children; IM is also being explored.

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- Adolescents seem to like CAB/RPV IM injections.

The cost of IV infusions poses challenges.

- Access to infusions is limited in RLS, including South Africa.
- Access is a challenge, even in high-income countries, as seen with mAbs used for COVID and ibalizumab for HIV.