HPV prevention and control in People Living With HIV
Benefits and Challenges of Immunobridging trials
DNA Methylation as a Triage Tool for Cervical Cancer Screening

Antwerp, Belgium (hybrid meeting)

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DISCLAIMER

"If you want me to give you a two-hour presentation,

I am ready today.

If you want only a five-minute speech,

it will take me two weeks to prepare."

Mark Twain

Context – HPV prevention and control in PLWHIV

- In WLWHIV, the burden of CC shifted to younger age, esp. in Sub-Saharan Africa
- In Sub-Saharan Africa – still a historic burden of children infected at birth – thanks to ART they live through childhood: target population for vaccination?
- HPV prevalence is high in PLWHIV; this will impact effectiveness of vaccination
- In older WLWHIV, impact vaccination is limited, therefore, better CC screening is necessary
- in PLWHIV; more hrHPV multi-infections, which may impact screening

Context – HPV prevention and control in PLWHIV

- ART contributes to a decrease in CC: increased regression of precancerous lesions, 60% decrease in CC incidence. However, the risk is still elevated relative to women without HIV
- In LMIC, only 15% of women are screened, far below WHO target of 70%
- Screening accuracy in PLWHIV
  - VIA: low sens, low spec
  - Cyto: high sens, relatively high spec
  - HPV: highest sens, lower spec -> higher spec with older age and with higher CD4 count

Context – HPV prevention and control in PLWHIV

- Concern of thermal ablation in WLWHIV. HCPs like thermal ablation but is it effective in WLHIV? The majority of studies have follow up data… We should look into persistence of HPV in WLWHIV after thermal ablation. Risk of using thermal ablation in cases of invasive disease

Context – HPV prevention and control in PLWHIV

- Vaccination of PLWHIV
  - WHO: 3-dose schedule
  - SA: 2-dose schedule, regardless of HIV status
- For PCV7, HIV+ reduces responsiveness and effectiveness
- For HPV – high conversion rates, limited data on effectiveness
- Anal CA still relatively rare but not evenly distributed: increase with age/longer duration of immunosuppression, higher in MSM
- Vaccination in MSM (18-26) to prevent anal CA: 1/3 HSIL at baseline [too late already?] However, no VT anal HSIL during FU in HPV-naive men

Context – Benefits and Challenges of Immunobridging trials

- Immunobridging studies to show that vaccines are equally immunogenic for children as for adolescents
- Need of standardized HPV serology to be able to properly compare between studies
- An internationally accepted standard of an HPV antibody level:
  - International Unit (IU), available for HPV 16/18, in development for other types in Gardasil9
- Reproducible methods for analysing readouts:
  - Parallell line method (PLL)

Context – Benefits and Challenges of Immunobridging trials

- bi- and quadrivalent HPV vaccines induce sustainable NAb levels to vaccine HPV types for up to 12-years
- NAb seroprevalence rates to HPV types 16, 18, 31, 33, 52 and 58 significantly correlated with reported VE against persistent infections
- In the people living with HIV bi- and quadrivalent HPV vaccines induce high rates of seroconversion
- Vaccine-induced cross-reactivity is diminished

Context – Benefits and Challenges of Immunobridging trials

- HPV-specific antibodies are detectable in FVU samples
- HPV-specific antibody concentrations detected in FVU correlate with concentrations in serum
- Non-invasive sample; home-based; likely preferred
- In Rwanda, despite sub-optimal coverage of birth-cohorts vaccinated during the catch-up, the expected CC reduction in these cohorts is around 60%
- Vaccine supply situation improved, due to Covid, missed vaccination of cohorts, fewer countries starting immunization programs
- SAGE advice: 1- or 2-dose can be used for 9-20 years; 2-d for 21+, at least 2-d, preferably 3-d for immunocompromised

Context – Benefits and Challenges of Immunobridging trials

- SAGE advice: prioritize catch-up of older cohorts and missed girls through MAC
- SAGE advice: males can receive same schedule as females
- Single-dose HPV vaccination is an attractive strategy in India, even if protection duration could be suboptimal
- With two-dose schedule, at least 26% more doses needed to prevent one cancer
- State-specific impact projections are helpful for national and state-specific policymakers in India

Context – Updates on one dose

- KEN SHE: excellent retention by M18; HPV 16/18 mITT efficacy 97.5% (2v/9v); HPV 16/18/31/33/45/52/58 mITT efficacy 88.9% (9v)
- DoRIS: seroconversion >98% for both genotypes; 1-dose immune responses non-inferior to studies where 1-dose efficacy was observed
- CVT: immunologic FU will continue to 20 years post dose 1 / PRIMAVERA: waiting for M36 results / ESCUDDO: final results expected 2024/2025 / PRISMA: will evaluate one dose in women aged 18 to 30 years - may allow for a massive, one-time catchup

Context – Updates on one dose

- IARC-India: long term protection is well-supported by immunogenicity data; adjusted VE against Incident & Persistent HPV 16/18 infections after 1D is similar to 2D/3D
- HOPE: measure the population impact of a 1-dose vaccine schedule, in protecting against infection with HPV 16 and 18; analysis in progress

Context – DNA Methylation as a Triage Tool for Cervical Cancer Screening

- Risk stratification, how to predict which lesions will progress?
- Women who were negative on cytology, HPV16/18 and S5 methylation were at low risk of progressing
- Useful triage test for women with CIN2, especially younger women who may wish to become mothers at a later stage
- Many different tests available, both commercial and research assays
- In WLWHIV, methylation followed by triage by cytology gives equal sensitivity/specificity, but potentially more objective results

Context – DNA Methylation as a Triage Tool for Cervical Cancer Screening

- Methylation of CIN2/3 correlates with higher p16/Ki-67
- Methylation of CIN2/3 correlates with lower E4 expression
- HPV positivity, HPV genotype and methylation status can be determined in one test
- Methylation levels In WLHIV are significantly higher than in HIV-women.

Lessons learned

- In future vaccine trials, include PLWHIV
- For anal CA screening, focus on risk groups
- For anal CA screening, HPV currently best choice, based on NPV
- Estimation of VE in adults living with HIV is challenging due to the seropositivity rates at baseline.
- Detection of HPV antibodies in FVU has the potential to complement vaccination registries in case of missing data
- There is no difference in attack rate in non-vaccine type HPVs; sterilizing immunity in KEN SHE, proof that it works

Lessons learned

- VLPs are highly immunogenic, like live viral vaccine, resulting in high affinity Abs. Due to IM administration with adjuvant better quality than Abs resulting from natural infection
- HPV type-replacement is not an issue as there is no competition between genotypes
- HIV care leads to better screening of WLWHIV than for HIV-
- In Sub-Saharan Africa, for anal CA, despite the issue with lower specificity, HPV detection is still the best option because of the NPV
- Recurrences after treatment are common: increasing tissue removal does not neccesarily reduce recurrence rates

Lessons learned

- Cytology is on its way out, methylation assays may be a replacement
- Methylation levels increase with disease severity
- Virtually all cervical cancers are methylation positive
- ½ of CIN2 and 2/3 of CIN3 cases show CC methylation pattern
- After long-term FU, methylation-negative women have better prognosis than cytology-negative women
- Methylation assays can be performed on both clinician-collected and self-sampled material, including urine
- Not all devices work equally well! And some may be less useful in LMIC circumstances

Lessons learned

- Chinese methylation study: after 4 years, 35% of HPV16/18+/methylation+ were CIN2+, versus only 1% of HPV-/methylation-. Is it time to use this to decide who to treat and who to FU after x years?

The way forward

- High vaccine coverage in WLWHIV is important, even if only at 1D
- Policy guidance needed from WHO in countries with high HIV
- Combine screening with vaccination
- Vaccinate earlier (before age 9), to give it before HIV exposure
- Study immunogenicity, protective efficacy and duration of protection, with reduced-dose schedules in immunocompromised individuals
  - In particular: protection when HIV seroconversion happens after 1 dose HPV vaccine

The way forward

- Need of implementation research to identify strategies to improve HPV vaccine coverage, including among populations at high risk of early HPV infection and immunocompromised individuals
- Perform cervical biopsies in HIV clinics to save time and reduce loss to FU. Not by central ObGyn, but by local, trained nurses/physician assistants, creating regional hubs, with easy access for entire districts
- See & treat strategy, but with biopsy to confirm appropriate treatment; in case of invasive disease, FU after 2-3 months
- Need of surveillance systems to monitor PLWHIV who are also HPV+ or could acquire the infection later on.

The way forward

- Check long-term effectiveness of ablative therapies
- Consider topical therapies

- When immunobridging, preferably to studies/populations with efficacy data
- Standards need to be anchored (peer-reviewers: ask for international units in manuscripts you review)
- Immunobridging studies should last at least 24 months for insight in immune response

The way forward

- Need for new Meijer guidelines for the use of DNA methylation tests as triage / primary screening test
- Provide strong data to support transition towards triage / primary screening by methylation assays
- Adapt methylation assays for use in LMIC: cost, self-sampling device, POC test
- Progression studies using methylation in WLWHIV needed, so far only cross sectional studies
- Validation studies needed: different populations; different sample types; different anatomic sites
- Different thresholds in different populations?

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Feedback welcome!

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HPV Prevention and Control Board

www.hpvboard.org