THE EFFECTS OF CD4⁺ LYMPHOPENIA ON THE HUMAN SKIN MICROBIOME

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BACKGROUND

- The role of specific immune responses in maintaining host-microbial skin homeostasis remains poorly understood.
- Previous data from DOCK (dedicator of cytokinesis)-8 deficiency, a primary immune deficiency characterized by lymphopenia, revealed expansion of skin virome in these patients.
- Lymphopenic people with HIV (PWH) frequently present with unusual skin manifestations of unclear origin and may also develop skin opportunistic infections like molluscum contagiosum; patients with idiopathic CD4 lymphopenia (ICL) also have frequent skin infections, predominantly related to human papillomavirus (HPV).
- It is unclear if the skin microbiome in lymphopenic PWH and ICL is perturbed and how this may relate to CD4 lymphopenia.

METHODS

- Skin microbiome topographical diversity (shotgun metagenomics) was analyzed in PWH, ICL and HIV-seronegative controls (HCs).
- Demographic and immunologic data were collected for all participants.
- The timeline of samples is depicted in Figure 1a, PWH were sampled at baseline prior to antiretroviral therapy initiation and after 2 and 15 months from ART initiation. Patients with ICL were sampled once and HC at three time points.
- Sampling from dry, moist, sebaceous and foot areas was performed as previously described (Figure 1b).
- Non-parametric test (Wilcoxon Rank-Sum) was used to determine the statistical significance of differences between the mean fungal and viral relative abundances across the cohorts and to compare the rate of change in skin microbiome shifts observed in the cohorts.

Figure 1a. Timeline of skin sampling in the 3 study groups

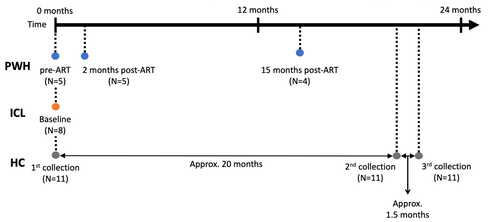
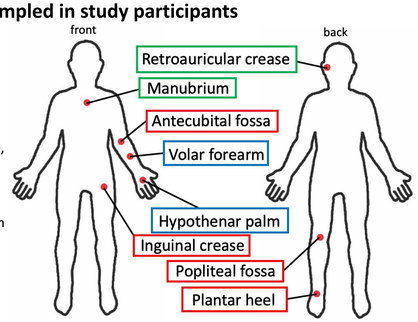


Figure 1b: Skin sites sampled in study participants

- Dry
  - Hypothenar palm, Volar forearm
- Moist
  - antecubital fossa, inguinal crease, popliteal fossa, plantar heel
- Sebaceous
  - retroauricular crease, manubrium



CD4 lymphopenia differentially affects the skin microbiome based on the underlying immunodeficiency:
ICL is more robustly associated with the expansion of the skin virome compared to HIV infection; on the contrary the skin mycobiome is expanded in PWH. ART can restore the skin microbiome in PWH

RESULTS

- 5 PWH (1 Black cis-female, 1 Black and 1 White Hispanic MSM, 1 White Hispanic cis male, 1 Black non-binary person) were recruited and sampled prior to ART; 4 participants were sampled longitudinally at month 2 and at 15 post-ART.
  - The median CD4 count and plasma HIV RNA was 48 cells/μL (IQR 16-83), and 361,206 copies/mL at enrollment, respectively, and 354 cells/μL (IQR 172-500) and <40 copies/mL at months 15 post-ART.
- 8 patients with ICL with median CD4 count of 65 cells/μL (IQR 22-81), were sampled. They were 7 White not Hispanic cis-men and 1 cis-female.

PWH: Clinical Diagnoses: Herpes (4), Thrush or esophageal candidiasis (3), Kaposi`s Sarcoma (3), Tinea or onychomycosis (3), Syphilis (2), Anogenital HPV (2), Cerebral Toxoplasmosis, Cryptococcosis, *Pneumocystis Jirovecii* Pneumonia, *H. Pylori* gastritis, *Clostridium Difficile* colitis, MRSA SSTI, bacterial vaginosis, epididymitis, latent TB, hypothyroidism, diabetes, seborrheic dermatitis. **Antimicrobials**: TMP/SMX (4), Fluconazole (4), Atovaquone (1), Valacyclovir (3), Ivermectin (5), Penicillin G (2), Terbinafine (3), Azithromycin (2), Levofloxacin (2), Metronidazole, Doxycycline, Bismuth, Linezolid, Ketoconazole, Imiquimod, Vancomycin, Bictegravir/emtricitabine/TAF (5).
ICL: Clinical Diagnoses: Skin warts and anogenital HPV (7), Dermatomal Shingles (3), Molluscum contagiosum (2), Cryptococcosis (2), Histoplasmosis, Coccidiomycosis, Herpes. **Antimicrobials**: TMP/SMX (5), Azithromycin (2), Fluconazole or Itraconazole (4), Valacyclovir (3), Podofilox, Peginterferon-α.

Figure 2: The skin microbiome of PWH and ICL is more heterogeneous than the one of HIV-neg controls; relative expansion of mycobiome was seen in PWH and of virome in people with ICL

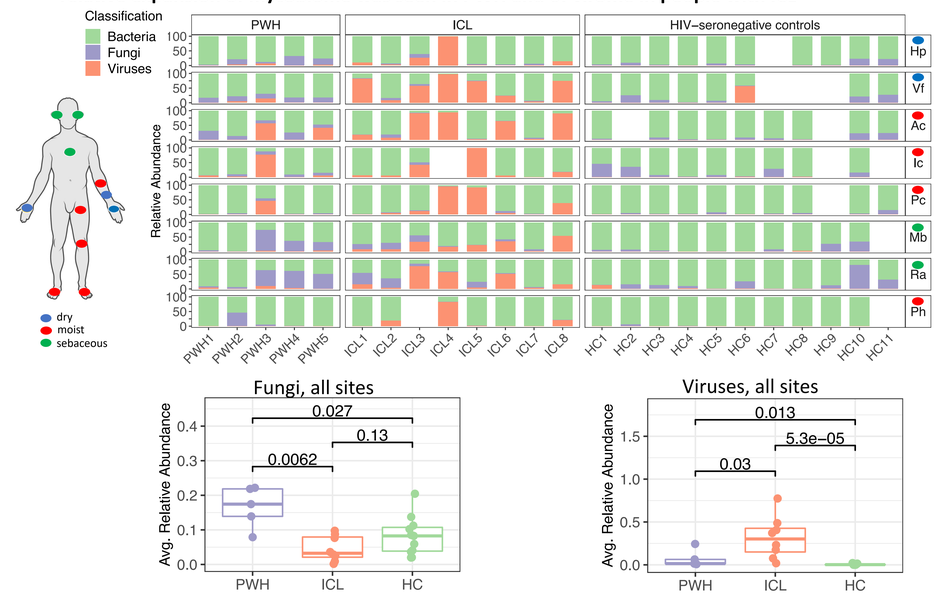


Figure 3: Representative examples of bacteria, viruses and fungi detected, and differences in HPV types in PWH vs. patients with ICL or HIV-neg controls

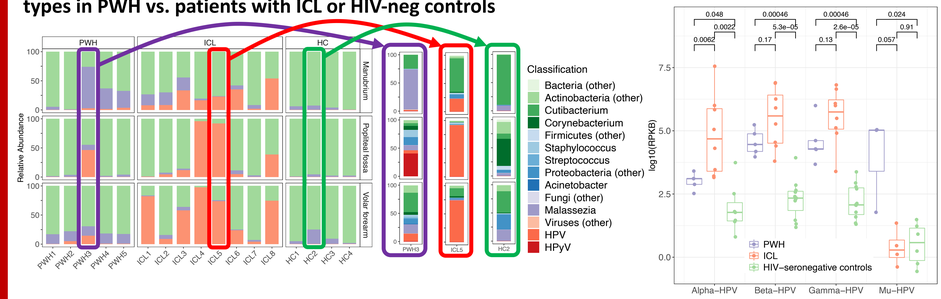
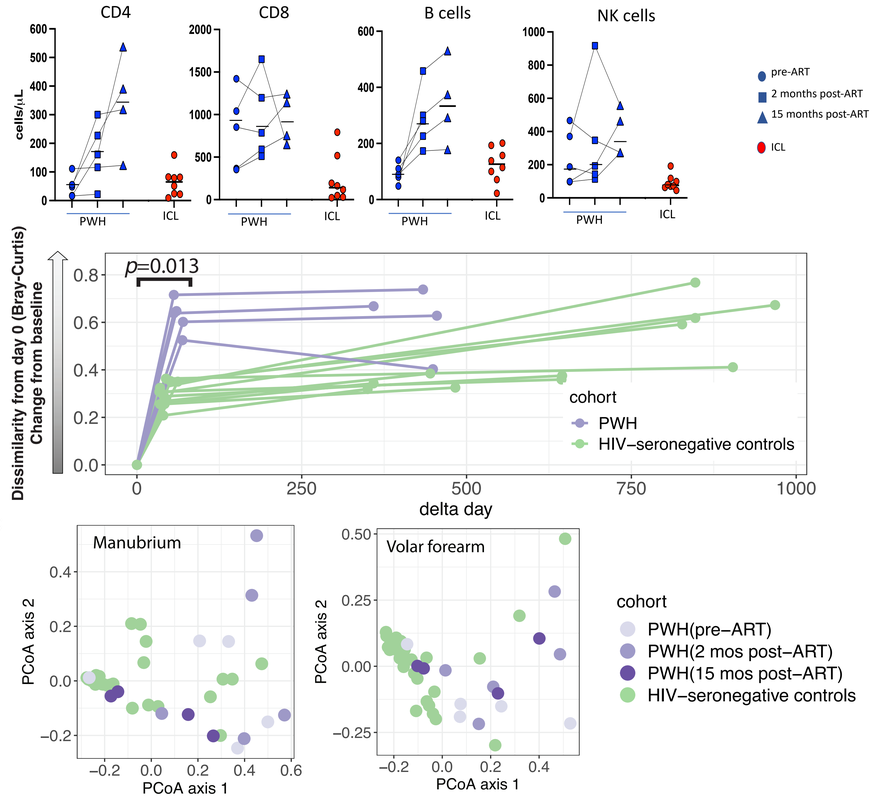


Figure 4: Antiretroviral therapy shifts the skin microbiome of PWH toward one similar to HC



CONCLUSIONS

- Significant expansion of skin virome is observed in people with ICL but not in PWH despite similar CD4 counts.
- Expansion of mycobiome is observed in PWH, ART initiation shifts skin microbiome towards one similar to controls.
- CD4 lymphopenia differentially affects skin microbiome based on underlying immune deficiency

References

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