Info-sheet #38 *from the series* ***"For a Better QL of PLWH!"***

ON THE WAY TO LONG-ACTING INJECTABLES

(the **XXX CROI:**
Conference on **Retroviruses** and **Opportunistic Infections**,
II, 2023, Seattle)
(translated from Latvian)

CROI still is the most scientific HIV conference in the world.
Along with its ~3000 scientists, 22 Community Educator Scholarship awardees were invited from all over the world.

The conference was held in the recently opened Convention Centre "Summit" building *(winner of the 2022 World Design Award)*, spread over several blocks *(it is hard to understand why was it built while across the street already exists a huge and contemporary Convention Centre "Arch").*
Once I was sitting in the lobby by a computer when a session in the big auditorium ended, and all the hundreds of its attendants were coming out. And then I felt the floor vibrating. The building's manager and its architect *(in a helmet)* who himself was still around to my worries answered that it is the way the edifice was intended!

Looking through the conference programme *(1005 abstracts in total)*, more than a third of its contents are devoted to SARS-CoV-2 and MPOX.

There is not much HIV news at this CROI, thus, very detailed analysis across many trials prevails. Though some scientists have felt ***underwhelmed*** about the conference, it has a wealth of useful information!

One of the CROI symposiums was on health and vaccine **mis-/ disinformation.** Traditional medical and public health organizations have communicated about the threat of SARS-CoV-2 infection and appropriate countermeasures *(e.g., masking and vaccines)* but were overwhelmed. This new reality of communicating health and science was called out by the WHO in 2020 as an **Infodemic.** *(Symp.9: Oral 46)*

Cure is still a long way off. During a Cure workshop, it was mentioned that "cure" may be too powerful and promising a term.
The major barrier to curing HIV infection is the latent **viral reservoir**. Antiretroviral therapy *(ART)* fails to fully restore immune function and is not curative, therefore, more effective therapies are required for PWH.

A cure for HIV has previously been observed in several individuals in which bone marrow transfer of **CCR5-modified stem cells** for leukemia treatment was also found to eliminate HIV *(e.g., Berlin patient).* But a more broadly applicable curative strategy is warranted. So, the transfer of autologous **CCR5-modified CD4 cells** has been found to be safe and well-tolerated in PWH. A single infusion of these CD4 cells led to a significant increase in CD4 cell count *(+162)* and reduced integrated HIV DNA in patients with maintained ART and control of plasma viremia for 1 - 6*(!)* years upon analytical treatment interruption *(ATI)* in 5 *(out of 9)* patients. This method can facilitate a functional cure for HIV. *(Oral 182)*

The same, a previously undefined group of **HIV-2** infected individuals – **extreme elite controllers –** *(EEC) (their investigation)* could spur novel functional cure strategies *(HIV-2 is less pathogenic compared to HIV-1, and HIV-2 infected individuals usually have undetectable or low plasma RNA viral loads while **HIV-1 elite controllers**: EC are quite rare).* *(Poster 244)*

And finally - on the transient use of tyrosine kinase inhibitors: TKIs may be applied to advance toward an HIV cure *[1-year treatment with **ponatinib** (a medication against chronic myeloid leukemia) resulted in the long-term protection of CD4 cells against HIV].* *(Poster 432)*

ART

Trial D2EFT has shown that in failing NNRTI-based 1st-line ART, **a switch** to either DTG + DRV/r or DTG + TDF/XTC *(tenofovir and lamivudine or emtricitabine)* was non-inferior in achieving viral suppression compared to DRV/r + 2NRTIs *(with DTG + DRV/r also achieving superiority). (Oral 198)*

LA-ART

Long-acting ART *(LA-ART)* with **cabotegravir *(CAB)* and rilpivirine *(RPV)*** was recently **approved in the U.S.**

LA-ART has led to virologic suppression *(VS)* in all 94 patients *(in San Francisco WARD86 HIV Clinic)* not initially suppressed. LA-ART *(and wraparound services)* may be indicated for patients with adherence challenges unable to achieve or maintain VS on oral ART. *(Orals 517, 518)*

According to SOLAR Phase 3b study, at month 11/12, CAB + RPV LA demonstrated non-inferior virologic efficacy vs B/FTC/TAF *(bictegravir/ emtricitabine/tenofovir alafenamide).* Changes in weight, BMI *(body mass index)*, and body composition measurements were minor and similar between trial arms. There were no clinically relevant changes in the proportion of participants with metabolic syndrome, abdominal obesity, or insulin resistance. Switching to injectable CAB + RPV LA from B/FTC/TAF was efficacious, well tolerated, improved treatment satisfaction, and was preferred by most participants. *(Orals 146; 191)*

Despite virologic suppression at the time of the switch to CAB/RPV, >25% of patients experienced at least one *(viral load)* VL>20 *(Univ. of California study).* *(Oral 516)*

And finally, *(according to the ATLAS-2M sub-study)* CAB and RPV parameters following 16 weeks of **thigh injections** were similar to **gluteal** administration. These results support rotational/short-term CAB + RPV LA IM lateral thigh administration within an established gluteal regimen. Overall, ~30% of sub-study participants *(38%: female sex at birth)* preferred thigh injections, largely, due to ease of access. *(Poster 519)*
We could only wish the price of LA-ART to go down for its wider accessibility.

A quantitative **VL categorization** is quoted by U.S. researchers:

- Undetectability < VLLV < 50 *(VLLV: very low-level viremia)*
- Low-level viremia: 51<LLV<199
- High-level viremia: 200<HLV<999
- Viral failure *(VF):* VL≥200 on 2 or more successive determinations or a single VL>1000. *(Poster 689)*

For example, the whole spectrum of **neurocognitive impairment *(NCI)*** was associated with worse viral control in PWH with a further higher risk of persistent LLV and VF in participants diagnosed with symptomatic NCI *(2010-2019 cross-sectional monocentric study).* *(P462)*

In a multicentre NAMACO study *(981 participants, median CD4=618, VL≤50),* age over 65 yrs was the only factor associated with a decline in neurocognitive performance. *(P 461)*

And lastly on viremia: unhealthy **alcohol use** is a major contributor to viral non-suppression *(VL>400)* among PWH *(SEARCH study's trial). (P 883)* Interestingly, in 2016, at the XXI WAC researchers from the first controlled alcohol administration experiment stated that VL and taking ART are not significantly associated with blood alcohol concentration *(BAC).(Infosheet#31)*

Other researchers provided evidence that a strategy of **nicotine replacement therapy *(NRT)*** and counseling are effective for smoking cessation in PWH leading to improved vascular health. *(P 654)*

The prevalence of any **depression** is significantly higher amongst people with HIV than those without it *(26% vs 11%) (as stated by COBRA cohort). (Or. 07)*

But, psychiatric symptoms are not associated with lower levels of ART adherence *(according to 2000 HIV study data).* *(Or. 472)*

And DTG use may increase depressive symptoms in older PWH, but not in PWH who are taking an antidepressant *(CHARTER project).* *(P 471)*

Higher MD - **muscle density *(less fat)*** was associated with a lower prevalence of coronary artery disease *(CAD),* while no associations between MD and physical function measures were apparent *(REPRIEVE trial). (P 648)*

Frailty is most commonly associated with falls *(PROSPER study)* *(P 698).*

A geriatric syndrome sarcopenia is associated with a loss of muscle mass and functionality. Its diagnosis was based on:

- Handgrip strength by a handheld dynamometer *(M:<28kg, F: <18kg)*
- Walking speed 4-m walk: <0,8 m/s
- Skeletal muscle mass. *(M: <7 kg/m², F: <5,7 kg/m²)*

Compared to negative controls, PWH had a higher prevalence of sarcopenia *(8,3% vs 3,1%)* and osteoporosis was almost double in PWH.
(Cross-sectional study, Thailand) *(P 696)*

The Wednesday Plenary was the first plenary on **aging** at CROI!
Comparing PWH *(45±15 y/o)* with PWoH *(people without HIV; 39±17 y/o),* the brain-age gap - BAG *(defined as the difference between brain-predicted age and true chronological age)* in PWH was positively associated with detectable viral load. *(Or.186)*

Haemoglobin measurements were categorized into:

- Mild: M: 11-13 g/dL; F: 11-12 g/dL
- Moderate: 8-11 g/dL
- Severe: <8 g/dL.

The **risk of death** was 6,4 times higher among PWH with *(vs without)* **anemia** *(NA-ACCORD: 67228 of PWH contributors).* *(P 688)*

Whereas the strongest predictor of all-cause **mortality** was current CD4<350 + VL>200 *(vs CD4≥500 + VL<200).* *(P 870)*

Non-AIDS-defining malignancies *(NADM)* are all cancers, except AIDS-defining ones *(Kaposi sarcoma, certain non-Hodgkin lymphomas, and cervical cancer).* The risk of NADM mortality was higher in participants that acquired the infection through heterosexual contact and ID use compared to MSM. *(CoRIS cohort, Spain)* *(P 871)*

An interesting revelation from the "New Diagnostics and Use of Tests" session. In the Houston area, a viral detection pipeline adapted from platforms developed to track SARS-CoV-2 was used to track **HIV in wastewater**. This work provides the first evidence that HIV can be detected in municipal wastewater systems, and has the potential to be developed into a new public health tool. *(P 947)*

To remember, times ago one pill a day seemed a dream…
Today, CROI provided insights into new **perspective** components in development: islatravir and long-acting lenacapavir with teropavimab and zinlirvimab. *(Or.193; 196; 197)*

Recalling what Anthony Fauci mentioned at the CROI Opening session: the **life expectancy** of 21 y/o person with HIV today is around +58 years!

Unexchangeably yours –
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