Infosheet #26 *from the series* ***"For a Better QL of PLWHA!"***

IF ONE COULD START IMMEDIATELY…

(the **XX CROI:**
Conference on **Retroviruses** and **Opportunistic Infections**,
Atlanta, III. 2013)

(translated from Latvian)

I shall start with a bit of the **CROI history**. Previously CROI was an annual gathering of American scientists, while the World AIDS conferences (WACs) gathered scientists from other parts of the world as well. When gradually WACs became more politically oriented, many researchers lost their "platform", and CROI became the most meaningful international conference in AIDS medical ield.
At the start of this CROI, the famous dr Kevin de Cock warned the audience that **not any CROI** can give something applicable in the clinical practice.
But let us see.

The most **out- breaking** news at this gathering was a **case of potential "functional cure" of HIV infection in an infant.** The doctor chose to immediately initiate *AZT, 3TC* and *nevirapine* (which was switched to *Kaletra* after 7 days) to this infant. Testing of the infant after a 5 month period off ART revealed a highly unusual outcome: VL remained undetectable (while there have been many studies of paediatric ART interruptions, all demonstrating that VL occurs rapidly, typically to very high levels). Immune responses to HIV were not detectable. Genetic studies showed that neither mother nor infant possessed the CCR5 mutation known to be associated with control of HIV replication. While the virus may not have been completely cleared after >10 months off ART no viral activity is detectable. This case echoes the one from the Berlin patient considered cured of HIV infection. Still, it remains possible that VL could rebound at some point in the future. Researcher D. Persaud has cited the possibility of studying triple cART instead of the normally recommended dual prophylactic regimen of *AZT* and *nevirapine* in infants with HIV+ mothers who have not received prophylaxis (the British HIV Association guidelines already recommend triple ART as post- exposure prophylaxis (PEP) for such infants Dr M. J. Seidner argues that this case represents an example of successful infant PEP against HIV infection rather than a cure of HIV infection..

Speaking on **immune restoration**, prior studies have shown slow and incomplete CD4+ T cell recovery for those starting effective ART with CD4<350 compared to those that start at a higher count. However, over time even those starting with low count may reconstitute to within normal range for HIV- person (CD4>500). The aim of British scientists (poster 311) was to investigate whether suppressive ART fully normalizes CD4+, CD8+ T cells, and CD4:CD8 ratio under

long term follow-up. Those in the lowest CD4 strata achieve CD4>500 over 11 years. But only those with a highest pre-ART ratio (>0,75) achieve normalization to ratio >1 over time, while individuals with a ratio of <0,5 at baseline never increment to >1 in the setting of sustained VL suppression and CD4 normalization.

In some studies the change from baseline in the CD4 count has been described to be greater in *lopinavir/r (LPV/r)* vs *efavirenz (EFV)* containing regimen despite a higher virological effectiveness of *EFV* arm. Spanish scientists have discovered (P310) that despite the difference in absolute CD4 increase between both regimens, the degree of immunological function restoration was similar in both groups. These data support that the differences in absolute CD4 gain with different cART regimen are not immunologically meaningful and explain the similar clinical efficacy of the regimens.

On mortality: US scientists (P309) report that HIV decreases CD57 expression on our beloved effector CD8+ T cells, which fails to normalize during ART, and strongly predicts mortality (as we knew already 20 years ago, there is enough of people with CD4=0, but none among us with CD8=0). Earlier ART and interventions to decrease monocyte activation may help reverse these defects, they say.

"**When to start**" is still the top discussion. The plausibility of potential benefits of treatment on diagnosis has been argued since *AZT* monotherapy. But at high CD4 count, there is too little evidence to know whether lifelong treatment is better than asymptomatic HIV infection. Currently, the evidence still supports equipoise for many people on the question of whether benefits outweigh the risks of earlier treatment at CD4>350. Results from the START study, expected in 2016, will provide the strongest real data to inform this question.
HIV+ people should have the option to start treatment at any CD4; especially to reduce the risk of transmission to sexual partners. But to be an informed choice, this needs to acknowledge that the evidence for personal health benefits at high CD4 has plausibility, but limited data.

Speaking of **new ARVs**, there are a number of ARV agents currently in development. These include:

- Newer agents in existing classes (e.g., integrase inhibitor *dolutegravir*)
- Drugs with new mechanisms of action, e.g.:
  - CD4 attachment inhibitors
  - CCR5/CCR2 antagonist (*cenicriviroc*)

The clinical use of the newer agents and formulations will depend on the results of clinical trials, concluded R. Gulrick from New York (oral 122).

And now, on the **neurocognitive** (NC) outcomes:

NC complications continue to afflict substantial proportion of people on ART. One explanation for this is ART neurotoxicity (NT).

Comparing *EFV* and *LPV/r* users, American scientists (P407) concluded that *EFV* users were less likely to have AIDS and detectable VLs in cerebrospinal

fluid, but had worse cognitive abilities: verbal fluency, speed of information processing, working memory and executive functioning. A potentially important interaction was identified that could indicate that the NT of specific ARV may differ based on HCV co- infection.

Frailty is significantly associated with several forms of cognitive impairments in HIV+ adults. American scientists (P444) recently found a significant positive association between HIV- associated neurocognitive disorders (HAND) and frailty. At baseline ~400 HIV + and HIV- participants had HAND or cognitive impairment, and ~50 HIV+ and HIV- had frailty. Within the 6 year study period, HIV+ and HIV- participants developed frailty at similar rates. There was no significant difference between those with vs without cognitive impairment. After controlling for age, HAND was significantly associated longitudinally with an increased incidence of frailty among HIV+ participants. The association between HAND and frailty was significant for HIV+ individuals after adjustment for age.

In their turn, Dutch scientists compared the BMD (bone mineral density) in:

- primary HIV infection (diagnosed within 6 months of the infection) with
- chronic HIV infection and
- HIV- controls.

DEXA scan results indicated significantly lower BMD in all three groups, compared to NHANES population dataset reference levels. However, there were no significant differences at any site, either by HIV status or duration of infection. Low BMDs at one or more sites were reported in 20%, 22% and 13% of the primary, chronic and control groups. In multivariate analysis, BMI was associated with low BMD at all sites but not HIV status.

Life expectancies (LE) of HIV+ individuals are increasing, but remain lower than in the general population and vary substantially between patient groups. The contributions of AIDS and non- AIDS deaths to lower LE remains unclear.
LE for some treated HIV+ individuals approaches that of the general population, but is significantly reduced in those starting ART with an AIDS diagnosis or with low CD4 count. While AIDS related deaths contribute substantially to these decreases in LE there is a persistent contribution of non- AIDS deaths to the shortened LE, American scientists conclude (P568).

As you see, CROI is highly scientific gathering (by the way, there are no pharma stalls, just posters in the exhibition hall).

Anyway, using this possibility, an interesting side thought on generics, finances and civil society. The existing **financing model of HIV civil society** is permanently unstable in the resource- poor world, and simply cannot continue in the resource- rich world, but no one is thinking about the financial implication of generics to HIV patient groups!…

To end on an optimistic note, here comes **gene therapy again**! French researchers (O 124) said that forthcoming trial results should open up the way to molecular therapeutics for ALL the infectious diseases that currently lack an effective treatment!

Permanently yours –
A.Kalnins, AGIHAS