Early ART Case Study: VISCONTI Cohort

**Purpose/Objective:** Participants can apply and reflect on the information learned in the early ART module presentation

**Materials:**
- Markers
- Flipchart
- Printed case study

**Method:** Group discussion

**To conduct this activity:**

**First**
- Explain the purpose of the activity to the learners
- If necessary, review and answer any questions related to key concepts of early ART (e.g. initiation of antiretroviral treatment during the acute phase of HIV infection)
- Explain that the VISCONTI cohort is only one example of an early ART study

**Second**
- Divide the participants into 2 – 4 groups, depending on the number of participants in the session
- Give the groups some allotted time to read and discuss their case study
- Be available in case groups have questions

**Third**
- Wrap up the session by asking a group leader to share the discussions and main conclusions of the group
- Write conclusions on the flipchart
- Ask other participants whether they understand and agree with the considerations
- Have members add additions or corrections until all of the major conclusions have been raised
Research Background
Post-Treatment Controllers (PTC), such as the VISCONTI cohort participants, present a durable control of HIV infection after interruption of treatment initiated at the time of primary infection. VISCONTI cohort participants are definitely different from HIV controllers who also present a natural viral control while they never received treatment. Differently from HIV controllers, PTCs presented a symptomatic primary HIV-1 infection, with a high viral load and a low CD4+ T cell counts. Most of them do not carry protective HLA class I alleles but rather neutral or high-risk alleles (such as HLA-B*35 or B*07) and have very weak CD8+ T cell responses. Levels of T cell activation are also higher in HIC than in PTC. Altogether, these parameters suggest that the mechanism of the viral control observed in PTC, although remains elusive, is different from those reported in HIV controllers.

PTCs also present strong specific antibody responses suggesting that B cell functions have been preserved. One of the major characteristics of PTCs is their very low level of HIV reservoirs measured by real time PCR quantification of total HIV DNA in CD4+ T cells. While in chronic treated patients, the CD4+ T central memory cells (T_{CM}) are the major contributors to the blood reservoir, in HIV controllers both T_{CM} and T_{TM} (transitional memory cells) subsets contributed equally to the HIV reservoirs. In PTCs, those long-lived resting CD4+ T cells (T_{CM}) contributed minimally to the HIV reservoir and might have been protected from infection by the early treatment.

Besides research on HIV eradication, studies on this remarkable status with durable remission may improve knowledge on functional specific immune responses.

The Scenario
In 2013, we reported a group of 14 Post Treatment Controllers (PTCs), also known as the VISCONTI patients (Viro-Immunological Sustained Control after Treatment Interruption). All of them have initiated cART during primary infection and for many years before stopping therapy.

Those case are rare but their frequency at 15% of patients early treated is clearly higher that the low frequency of HIV controllers (less than 0.1% of infected patients).

They all maintain a viral control and very low level of viral reservoir a long time after treatment interruption. French scientists are now following twenty cases with a median time of remission of 9.3 years, with the longest period of control of more than 12 years so far (range: 4.5 –12.5).

Issues
PTCs represent the proof-of-concept of HIV durable remission induced by antiretroviral treatment. Besides research on HIV eradication, the objective to induce a durable remission seems a realistic goal in the medium term. Understanding of the mechanisms underlying such a durable viral control will help gain knowledge on HIV pathogenesis and define markers that could help to identify candidates to PTC status.

To increase the number of remission cases represents also an interesting goal; that needs promotion and access to early diagnosis, to be in a position to rapidly start treatment.

Actions
1. To facilitate patho-physiological studies to delineate the mechanism of the viral control
2. To increase the numbers: to initiate systematic and early therapy in all acute infections
3. Treatment interruptions are not recommended: they must be organized within standardized and controlled clinical trials.
4. Complications: risks of transmission to partners after treatment interruption in case of viral rebound
Case Study Questions:
1. Can you name some of the ethical considerations and implementation challenges for studies such as the VISCONTI cohort?
2. Could we increase the frequency and the numbers of PTCs in remission, with early treatment?
3. Could we identify markers before treatment interruption to select the best candidates for the PTC status?

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Discussion Guide

Question 1:

Can you name some of the ethical considerations and implementation challenges for studies such as the VISCONTI cohort?

Example ethical considerations provided in the PowerPoint include:

- How early is “early enough”?
- Early ART will not be curative, so we need to be careful about the language used at all times. There is a risk of curative misconception.
- Treatment interruptions are not medically recommended. For early ART studies, these need to be standardized and closely controlled and monitored.
- We must also consider whether early ART patients are considered “vulnerable” or “healthy” and what the social perceptions are vs. the actual medical vulnerability and risk of HIV transmission to sexual partners during the acute phase of HIV infection (when viral load is high).
- There may also be potential impacts (both positive or negative) on interpersonal relationships of being in an early ART study (e.g. early diagnosis, resilience, efficacy towards study involvement, etc).
- Treatment interruption may also be a problem for HIV transmission.

Some of the implementation challenges of early ART studies include:

- It is difficult to identify people in the acute phase of HIV infection.
- Recruitment efforts take a long time. Most studies have been small due to date, although the OPTIPRIM study (Lancet ID) includes 90 patients.
- Scientists also need to determine the best time point to initiate ART (the earlier the better).
- At this time, it is difficult to compare studies of early ART, because scientists have used different timing of ART initiation and ways to measure the reservoir.
- There is some variability between how patients respond to early ART.
- There are also concerns around scalability of this HIV cure research method on a global scale, due to the difficulty of identifying patients in the early phase of infection.
  - 4-week window when HIV IgG AB not yet detected by standard assays
  - Diagnosis of AHI requires NAT (costly)
  - Patients consult physicians at the time of symptoms (e.g. Fiebig stages III – V) (Hocqueloux JAC, 2013).
Question 2:

Could we increase the frequency and the numbers of PTCs in remission, with early ART?

Considerations include but may not be limited to:

- It is difficult to identify individuals in the acute phase of HIV infection. There is a 4-week window when the HIV IgG Ab is not yet detected by the standard assays, so the diagnosis requires Nucleic Acid Testing (NAT), which is costly.
- We must also rely on the Fiebig stages. Patients also tend to consult their physician at the time of symptoms (e.g. Fiebig III to V). It may be difficult to implement systematic NAT testing for individuals at higher risks for HIV infection. Other individuals, not part of the “higher risk groups,” may also be in the window period but may be missed during the acute phase of HIV infection because not everybody has strong symptoms.
- These studies take a long time to complete. As reported in the case study, the longest period of control is more than 12 years so far. If we include the number of participants, we do so with the understanding that it will take a long time to collect the longitudinal data. These studies are also costly.
- Treatment interruption for PTCs still requires careful and close monitoring to look for viral rebound. Participants must also consent to treatment interruption and to frequent study visits and blood draws. Their partner(s) may also need to be aware of their participation in the study, since there could be a risk of HIV transmission to the partner(s) if there is viral rebound.
- To ensure that we have comparable data, new participants should be treated within the first 2 months of HIV infection (as with the initial VISCONTI cohort participants). However, we know that the earlier we start treatment, the better since the HIV reservoir is seeded almost immediately. So new participants may initiate ART at different time points in the course of their HIV infection and we must have a way to deal with this variability in the data.
**Question 3:**

**Could we identify markers before treatment interruption to select the best candidates for the PTC status?**

Considerations include but may not be limited to:

- Yes, but in general, we need more research to understand the mechanism of viral control for PTCs.
- We know that VISCONTI cohort participants had no protective HLA class I alleles – but neutral and high-risk alleles. They also had weak CD8+ T cell responses and thus no favorable genetic profile.
- We also know that lower HIV DNA levels and shorter time to ART initiation from onset of HIV infection predicted PTC.
- Search for biomarkers must also translate into clinically meaningful results.
- Biomarkers of HIV rebound kinetics may be helpful in early phase studies but there can be fewer participants and several possible biomarkers; studies may have limited power.
- Per the CROI 2015 conference, we also know that PTCs have particular NK cells with high anti-HIV capacity. NK cells from PTCs may have a particular phenotype and a higher capacity to control HIV infection. More research is needed on the immunological aspects of PTC.