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PERSPECTIVE



# Enhancing care for people living with HIV: current and future monitoring approaches

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**ABSTRACT**

**Introduction :** Antiretroviral therapy (ART) is the most significant advance in the medical management of HIV-1 infection. Given the fact that HIV cannot be eradicated from the body, ART has to be indefinitely maintained. New approaches need to be defined for monitoring HIV-infected individuals (PLWHIV), including clinical, virologic, immunological parameters and also ways to collect individual points of view and quality of life.

**Areas covered :** We discuss which tests may be used to improve the management of PLWHIV and respond to a comprehensive health demand.

**Expert opinion :** Viral load and CD4 counts are well-validated outcome measures and we still need them, but they do not completely depict the health status of PLWHIV. We need to better understand and to apply to clinical practice what happens in sanctuaries, what is the role of HIV DNA, what is the meaning of low-level viremia. Most of these questions do not yet have a definitive response. Further, we need to understand how to modify these variables in order to improve outcomes.

Similar points may be raised for immunological measures and for tests exploring the tolerability of drugs. The goal must be the evolution from a viro/immunologic-based to a comprehensive quality-of-health-based evaluation of PLWHIV.

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HIV; antiretroviral therapy; surrogate markers; surrogate endpoints; patient Related Outcomes (PROs)

## 1. Introduction

Antiretroviral therapy (ART) has dramatically changed the life expectancy of people living with human immunodeficiency virus (PLWHIV) [1].

Modern ART, both in naïve and in pre-treated subjects, leads to very high virologic success rates, with minimal differences in efficacy rates shown in clinical trials among different available drug combinations if measured according to current standards in terms of viral decay and CD4+ increase [2].

Since the introduction of the most recent INSTI-based (integrase inhibitors) regimens, more rapid viral suppression, high virologic success, and low to no selection for resistance have been achieved further limiting the possibility to pinpoint differences [3].

However, even within this scenario with long-term, effective ART, PLWHIV experience negative events that can include persistent or sporadic low-level viremia, persistent low-grade inflammation, and immune activation. These events are strongly associated with a heightened risk for cardiovascular disease, osteoporosis, frailty, among other non-AIDS–defining events, and may explain why life-expectancy of PLWHIV remains lower than that of general population [4].

Until now, the effectiveness of ART has been measured by clinical endpoints, or standardized surrogate markers that allow, for example, the definition of non-inferiority in clinical trials. These markers fail to address the lingering effects of HIV. New ancillary markers should be developed and implemented, to support clinicians in the framing of each individual patient and to forecast outcomes in terms

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**Article highlights**

- Plasma HIV-RNA is a consolidated measure to monitor the efficacy of antiretroviral therapy, but we are currently unable to effectively measure HIV reservoirs. Although other biomarkers are available, they lack either clinical validation or feasibility in routine clinical practice. HIV-DNA, next-generation sequencing, and phenotypic drug resistance have a high scientific rationale. However, their feasibility is still at medium-low level, which is a challenge for future monitoring in PLWHIV.
- Increased immune activation and inflammation are hallmarks of HIV infection and are only partially restored by virally effective ART. Residual immune activation while on effective ART seems to be a multifactorial event, possibly resulting from the combination of co-infections, residual viremia, and microbial translocation. Despite the fact that several cohort data have shown an association between markers of immune activation/inflammation and the development of clinical events, a definitive clinical validation of pro-inflammatory markers is still lacking.
- Dramatic improvements in terms of morbidity and mortality have followed the introduction of ART turning HIV infection into a chronic disease. However, the aging of PLWHIV, the growing proportion of new HIV diagnosis among older people and the long-term use of ART have been associated with the development of non-infectious, non-HIV related comorbidities. Furthermore, cardiovascular complications, weight gain, bone disease and neurocognitive disorders are frequently observed and show distinctive patterns in PLWHIV. This situation both requires the validation of markers already used in the general population and the development of new and more specific ones.
- A '*patient-centered medicine*' must be based on patients' reported outcomes (PRO) measures as key elements for identifying the unmet needs of patients and to manage current gaps with the general population. PRO measures and, in particular, Quality of Life could represent new direct clinical outcomes for identifying significant differences among drugs. How to implement PRO measures in clinical practice should represent a key aspect of the strategic management of PLWHIV.
- The goal is not to abandon the evidence-based monitoring tools already in place, such as CD4+ T cell count and viral load determinations. The aim is to develop technologies and tools that will make new markers and goals available so to come to a comprehensive, individualized, and more precise management of PLWHIV that could be affordable, accessible, and acceptable.

of long-term efficacy, safety, and quality of life. Beside these medical concerns, PLWHIV often continues to face many of the same challenges that made them vulnerable to acquiring HIV (limited health literacy, lack of access to care, stigma, and dependency from recreational drugs). Although primarily designed for research purposes, Patient-Related Outcomes (PROs) should be considered an essential part of monitoring [5] and should become a standard part of any medical history and mandatory outcome measures in both clinical trials and every-day practice. The fourth '90' – measuring quality of life – goes beyond the established UNAIDS 90–90-90 targets and it is essential to face HIV-related health challenges and factors such as overall physical and mental well-being and HIV-related discrimination experiences.

For these reasons, it is necessary to go further and identify new and more precise criteria to define the success of ART therapy. These criteria should be as personalized and innovative as possible, making the most out of advances of science.

Although several innovative markers and tools have been proposed to better define the overall success of ART in the last few years, there is yet no consensus about which ones are most useful or relevant in clinical practice.

The time has come, to define the most appropriate diagnostic tools to define what successful ART looks like, as CD4 + counts and HIV-RNA loads are no longer enough [6] to correctly frame future challenges.

The objective of this review is to provide a comprehensive overview of what are the current and future indicators that will help physicians to personalize ART. It also describes their strengths and weaknesses, eventual current limits to their widespread use in clinical practice, but also the research opportunities they offer and the future developments for every-day care.

## 2. Virology

### 2.1. Current status

Virologic monitoring has been the fundamental measure of ART success, both in clinical trials and in clinical practice for more than 20 years [7]. Current assays can quantify HIV RNA down to as few as 20 copies per milliliter of plasma and indicate whether there is any detectable virus below that level. However, due to extensive use of previous generation assays with a 50-copy threshold, achieving <50 HIV RNA copies/ml is the reference definition of virologically successful ART, and patients experiencing this status are often referred to as virally suppressed. The second component of routine virologic assessment of ART has been drug resistance testing. Initially proposed as a research tool, resistance testing through HIV genotype analysis was soon introduced into clinical routine and became an integral part of ART management [8]. Despite the recent decreasing impact of HIV drug resistance in resource-rich countries [9], detection of transmitted and emergent resistance has been and still is a key information for guiding ART choices at both the individual and population levels. Drug resistance testing has been extended to latent HIV DNA, rather than just replicating RNA, allowing resistance information to be obtained from PLWHIV who have virologic suppression in specific contexts such as before treatment switch [10].

While ART success has allowed most patients to have undetectable HIV RNA and no drug resistance, novel techniques allow exploration of new potential markers and standards for successful, lifelong ART, with the possibility to reduce drug pressure while maintaining effectiveness and, perhaps prepare patients for HIV eradication studies (Table 1).

### 2.2. Gaps and unmet needs

The key question, in current management of HIV infection, is what kind and extent of viral suppression is required for long-term patient safety and to allow possibly future treatment approaches such as deintensification and curative strategies. The question does not only involve a deeper analysis of the easy to reach blood compartment, but also an investigation of

**Table 1.** Virology.

| ITEM | Validated in non-HIV areas (Y/N/NA) | Validation status HIV (H/M/L) | Outcomes | Setting (research/clinical extensive/clinical target population) | Feasibility (H/M/L) | Barriers | | | | | | Ref. (nr.) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Complexity | Cost | Large volume of blood required | Clinical correlates poorly/incompletely defined | Instrument availability | Biosafety | |
| HIV RNA target detected (TD) vs. not detected (TND) | NA | M | Higher risk of virologic failure for patients with TD as compared with repetitive TND | clinical extensive | H | | | | | | | 12, 14 |
| HIV RNA Single-copy assays (SCA) | NA | L | Undefined for routine clinical ART monitoring; may have relevance for eradication studies | Research | L | ■ | ■ | ■ | | | | 11, 16 |
| Quantification of total HIV DNA | NA | M | Higher risk of failure of the first-line regimen; still undefined for routine clinical ART monitoring; still unclear if it mirrors the dimension of HIV reservoir | clinical target population | H | | | | ■ largely represents defective genomes | | | 17-20 |
| Cell-associated HIV RNA (CAR) | NA | L | Should measure residual HIV activity (replication-competent reservoir) | clinical target population | M | ■ | | | | | | 23 |
| Next generation sequencing (NGS) | Y (human genetics, microbiome studies) | H | Identification of minority variants | clinical target population | H | ■ | ■ | | | ■ | | 24-27, 29 |
| Phenotypic drug resistance testing | Y (bacteriology) | H | May help defining drug resistance in very complex situations or for new drugs | clinical target population | L or M according to country | ■ | ■ | | ■ Clinical correlates uncertain for selected drugs (e.g. dideoxynucleoside analogues) | | ■ | 8, 30 |

Y = yes; N = no; NA = not applicable; H = high; M = medium; L = low; ■ applies to the item

the status and dynamics of the HIV reservoir within the lymphatic tissues and possibly other sites.

Additionally, in the marginal, but challenging, set of patients with a high burden of drug resistance and uncontrolled virus replication, there is an urgent need to define procedures for patient profiling and treatment strategies, best administered by a multidisciplinary team covering the different aspects of this population.

### 2.3. Perspectives

An immediate opportunity to virus suppression beyond the reference 50-copy threshold is the discrimination between target detected (TD) or not detected (TND), a result returned by currently used HIV-RNA assays when the analyte is below the threshold of quantification (actually ranging from 20 to 40 copies/ml in the most common platforms). While assay reproducibility is poor at the TD/TND limit [11], a number of population studies have suggested that TD and TND have different rates of virological failure over time [12], particularly when the TND status is confirmed across multiple time points [13]. So far, guidelines do not clarify how to use TD/TND data, but this parameter has been recently used in clinical trials to evaluate efficacy of 2-drug combinations and triple therapies [14,15]. On the other hand, despite recent improvements, the use of investigational single-copy assays to quantify residual HIV RNA well below the threshold of the routine assays is likely to remain in the research setting, mainly due to cost, current lack of standardization, and the large volume of blood required [16].

In the context of HIV-RNA suppression, quantification of total HIV DNA in blood cells is being increasingly considered as a surrogate marker of the size of HIV reservoir [17]. Although, HIV DNA was originally described as a prognostic marker of disease progression in the absence of treatment, its role can be currently envisioned in both guiding and monitoring the effects of treatment de-intensification or to select patients for pilot eradication studies. Although total HIV DNA includes different HIV-DNA species likely to have different meanings, a correlation between total and inducible reservoir measurement has been reported through the viral outgrowth assay [18]. Commercial kits for quantification of total HIV DNA have been released by small biotech companies and are expected to be developed by large diagnostics companies. However, guidelines for the use of total HIV DNA remain to be established and further discrimination between different species (integrated vs. unintegrated [19]) and status (replication competent vs. defective [20], inducible vs. non-inducible [21]) appears to be feasible but far from clinical application at this time. Likewise, differentiating the extent of clonally expanded HIV DNA as a result of homeostatic proliferation from single integrants representing *de novo* infection remains an appealing option currently limited, however, to the research setting [22]. Nevertheless, detailed characterization of HIV DNA extracted from blood lymphocytes or lymphocyte subsets hold promise for profiling the HIV reservoir at an individual level and for supporting patient-tailored treatment strategies. Strengths of this approach include ease of sampling and DNA stability. However, technological advancements are eagerly awaited to expand knowledge, increase the feasibility and define clinical application guidelines.

Similar to HIV DNA, cell-associated HIV RNA (CAR) in blood has been recently proposed as a marker of residual HIV activity in virally suppressed patients [23]. Assays have been developed in the academic setting and are not commercially available; however, adaptation of systems certified for plasma HIV-RNA quantification can be attempted. Theoretically, more effective ART should be associated with lower CAR levels and CAR could be analyzed together with other indicators of the HIV reservoir (e.g. HIV DNA) and residual HIV replication (e.g. TD/TND) to build a full molecular picture of the patient's status. Again, similar to HIV DNA, CAR is actually a mixture of many different species, such as differently spliced mRNAs, but differentiating among all of them appears to be very challenging. However, a rough distinction between un-spliced (a surrogate of full replication) and spliced mRNAs (representing a variety of regulatory functions) is possible but not yet clearly interpretable [21]. If it is true that one of the old maxims of medicine is 'don't order a test if you don't know what you'll do with the result,' researchers have still a lot of work to carry out with most of the assays discussed here before they could become available and useful clinically.

Despite the extensive and successful use of genotypic drug resistance testing based on Sanger bulk sequencing,

development of next-generation sequencing (NGS) at an impressive pace has recently fueled the debate whether higher resolution NGS should replace bulk sequencing in the clinical setting [24]. Initial arguments favoring NGS have mainly focused on the ability to detect minority drug-resistant species before ART start. Indeed, minority species detected by NGS but not by bulk sequencing can impair response to treatment, particularly to NNRTIs [25]. However, the almost complete transition to first-line ART based on high genetic barrier anchor drugs makes this potential value hardly appreciable and is even questioning the role of standard bulk sequencing in this setting. By contrast, management of patients with a complex history of drug resistance can benefit from high-resolution NGS providing a more comprehensive picture of the drug resistance species and guiding treatment choices, both in the viremic and virally suppressed patients [26,27]. Along with the development of cost-effective NGS systems certified for diagnostic use, it is anticipated that high-resolution resistance testing will become an integral part of the clinical profiling of such patients. This will allow to draw a more precise picture for drug resistance surveillance [28]. The added value of NGS has been demonstrated, in limited resource settings, in the context of a treatment-as-prevention trial, where the majority of subjects received a 3-drug EFV-based (efavirenz) regimen [29].

In addition, viremic patients harboring multidrug resistant virus with complex mutational patterns, particularly in the context of low CD4 counts and increased risk for clinical progression could benefit from phenotypic drug resistance testing, e.g. to detect residual drug activity for one or more drugs and help to build a new effective regimen when a novel drug class becomes available [30]. Phenotypic testing is routinely available in some countries, but in other regions, due to limited availability, technical challenges and requirement for biosafety containment, phenotypic testing remains confined to the research setting and limited routine practices.

A general limitation of all of the currently available and future candidate markers is the almost exclusive application to the blood compartment. While the analysis of blood markers has clearly allowed establishment of highly effective treatment strategies, the vast majority of HIV species reside in lymphatic tissue in multiple anatomical sites that are hardly accessible [31]. Although blood will necessarily remain the material of choice in routine patient management, studies addressing the added value of sampling these sites are required to gain a full profile of the HIV reservoir and its dynamics under different treatment strategies. Ideally, blood markers matching clinically relevant features in the comprehensive HIV reservoir should be discovered and validated to provide novel guidelines for patient-tailored interventions aiming at defining the most convenient compromise between treatment tolerability and effectiveness in the long-run as well as selecting candidates for future HIV eradication strategies.

## 3. Immunology and Inflammation

### 3.1. Current status

Inflammation and immune activation have been long considered hallmarks of HIV infection, that are only partially reduced after ART induced virologic suppression, therefore persisting at levels significantly higher than in HIV-uninfected individuals [32].

Successfully treated PLWHIV still present an increased risk of non-AIDS-related diseases, such as cardiovascular disease (CVDs), cancers, diabetes, and neurocognitive disorders [33]. Given the degenerative/inflammatory nature of such clinical conditions, the hypothesis of a cause–effect relationship between the excess of non-AIDS morbidity/mortality and the ensuing hyperactivated immune status during suppressive ART has been long postulated.

### 3.2. Gaps and unmet needs

Despite numerous data from cohort studies, a clear and incontrovertible link between inflammation/immune activation and the increased risk of non-AIDS-related diseases is still lacking, and several questions need to be answered. Immunometabolic signatures that combine markers of immune activation/inflammation and metabolic profiles have been proposed as predictors of non-AIDS comorbidities in PLWHIV under ART. Indeed, the observation that several biomarkers are associated with specific morbidities and, on a broader scale, to mortality have focused the research on those clinically significant biomarkers that could be modified with effective interventions once abnormal levels are observed. Despite great enthusiasm toward the possible clinical role of immune activation/inflammation biomarkers, to possibly estimate the risk of disease progression in the setting of successfully treated infection, we are still far from their concrete exploitation in the clinic, due to several intrinsic limitations (Table 2). Amongst these are the wide biological variability of biomarkers and the paucity of interventional studies performed to validate their potential clinical application.

### 3.3. Perspectives

Among pro-inflammatory markers, IL-6 and D-Dimer have shown to be independently associated with non-AIDS co-morbidities and mortality in PLWHIV, suggesting that treatment aiming to decrease these biomarkers may help to reduce morbidity and mortality. It has also been shown that intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, known as markers of CVDs, are elevated in PLWHIV and are associated with atherosclerosis and vascular inflammation. More recently, the introduction of omics-based technology provided new targets potentially useful to identify pathophysiological mechanisms underlying increased morbidity in PLWHIV. Specifically, by using an untargeted metabolomic-approach, machine-learning prediction of metabolites changes indicated higher risk of inflammatory and neurological diseases in PLWHIV [52]. Metabolic abnormalities were observed in amino-acid levels, energetics, and phospholipids and complex lipids, resembling immune-aging, and metabolic syndrome.

Cerebrospinal fluid levels of neopterin and neurofilament light protein (NFL) and, potentially, serum levels of NFL once clinically validated, provide additional information in the

setting of central nervous system inflammation and neuronal damage.

Several markers of monocyte/macrophage and dendritic cell (DC)-driven inflammation have been investigated. Amongst these, sCD163, one of the more interesting, has been associated with all-cause mortality and non-AIDS morbidity in large cohorts of ART-treated patients [53] as well as cerebral, lung, and cardiovascular events [54]. The quantitation of interferon (IFN) type 1 molecules, by means of new technologies, could result relevant in the context of primary infection [55].

Speaking of lymphocyte activation, a consolidated bulk of evidence have demonstrated enhanced T-lymphocyte activation in untreated HIV infection, with raised levels of CD38+ HLA-DR +CD8 + T-cells. The same alteration has also been associated with disease progression and this T-cell hyperactivation is only partially reduced by long-term ART and never lowers to values detected in HIV-uninfected individuals [32]. Interestingly, while studies in resource-rich settings show that persistent T-cell activation has a poorer clinical prognostic power than monocyte/macrophage-related inflammation, in PLWHIV on virally effective ART [56], the contrary has been proven in resource-limited settings, where infectious complications still remain a prevalent cause of death [57].

Beyond T cell, other cell types have been studied as alternative biomarkers of progression: Natural Killers (NK), monocytes (Mo), MAIT and dendritic cells (DC). Among Mo, non-classical and intermediate Mo seem to be increased in PLWHIV with cardiovascular events and neurodegenerative disorders [58], whereas a reduction of plasmacytoid DC has been associated with virologic failure and disease progression [59]. Despite several data have shown alteration in the frequency and function of NK, NKT MAIT, and innate lymphoid cells in PLWHIV, the possible role of such cell subpopulations in predicting HIV-associated morbidity and mortality have not been investigated [60–62].

Several pathogenetic mechanisms have been proposed to explain the persistent immune activation/inflammation in patients on virologically suppressive ART, but a full understanding of the underlying causes is still lacking and deserves to be extensively addressed. Several studies in recent years have focused on the role of viral co-infections, residual viremia, and microbial translocation. Research data show that the systemic translocation of bacterial by-products through a damaged gut mucosal barrier, mainly lipopolysaccharide (LPS), are major drivers of continuous immune stimulation. Consequently, several markers indicative of gastrointestinal damage (e.g. LPS, bacterial rDNA, IFABP, zonulin, kynurenin/tryptofan ratio) and of microbial translocation (MT)-driven inflammation (e.g. sCD14) have been associated to different clinical comorbidities, during ART, in cohort studies. None of them have, however, been validated [63,64]. Specifically, whether or not markers of MT independently predict disease progression after ART initiation is still under debate.

Viral co-infections have been proven to substantially contribute to persistent immune activation. Under this perspective, the presence of cytomegalovirus (CMV)-antibodies have been indicated as a proxy of immune activation and of CMV continuous stimulation. Since the beginning of the HIV epidemic, several studies have demonstrated that a positive CMV serology is a negative prognostic marker in both untreated and treated PLWHIV [65]. The quantification of CMV antibodies, and in some cases CMV-DNA, seems to be related to cardiovascular events even though a threshold has not been defined also because of the different quantitation methodologies used [66].

Despite great enthusiasm toward the possible clinical role of immune activation/inflammation biomarkers, to possibly estimate the risk of disease progression in the setting of successfully treated infection, we are still far from their concrete exploitation in the clinic, due to several intrinsic limitations. Amongst these, the wide biological variability of biomarkers and the paucity of interventional studies performed to validate their potential clinical application.

The lack of consolidated data on the role of immune activation/inflammation biomarkers together with the technical complexity of their measurement and the absence of clinical validation of such biomarkers have, somehow, diverted the scientific attention toward an old and yet very reliable immune marker: the CD4/CD8 ratio. Indeed, CD4/CD8 T-cell ratio has been inversely associated with markers of immune activation, suggesting that it might capture the HIV-driven immune dysregulation [67]. Nevertheless, while several cohort studies have proven its association with disease outcome [68], most recent data, on very large patients' cohorts, have failed to find any association between CD4/CD8 ratio and all-cause mortality [69], questioning its effective exploitation in the clinical setting.

## 4. Comorbidities

### 4.1. Current status

The prevalence of chronic non-communicable diseases, or co-morbidities, among PLWHIV is increasing in recent years as a consequence of aging, chronic inflammation, systemic immune activation, and long-term exposure to ART (Table 3).

### 4.2. Cardiovascular aspects

Current guidelines [71] suggest utilizing risk-assessment algorithms (Framingham, ASCVD, D:A:D, etc.) to estimate cardiovascular risk. Although these equations are useful, they may underestimate the real risk for individual PLWHIV [72,73].

### 4.3. Weight gain

The lipodystrophy syndrome has represented one of the most impacting long-term adverse events of first-generation ART including protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs). Recent studies have highlighted the risk of weight gain (WG) among PLWHIV starting ART [74]. Among available anchor drugs, the integrase inhibitors (INIs) have been associated with a higher risk of WG with respect to PIs and non-nucleoside reverse transcriptase inhibitors (NNRTI)

Table 2. Immunology and Inflammation.

| Item | Use in other fields | Validation in PLWH | Outcomes | | | | | | | | | Setting (research/clinical extensive /clinical target population) | Feasibility | Barriers | | | | | | | | Ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Survival | AIDS events | Non-AIDS events | CVD | Metabolic | Neurological | Cancers | CD4 recovery | HIV control | | | Multiple confounders | Non standard methods | Expertise needed | Small sample | Poor specificity | Lack of threshold | Uncertain causality | Lack of interventions | No clinical effect | |
| CD4/CD8 | Y | H | ■ | ■ | ■ | | | | | | ■ | Clin Ext | H | | | | | ■ | ■ | ■ | | | 50-51 |
| T cell activation | Y | M/H | | | ■ | | | | | ■ | ■ | Res/Clin Ext | M/H | | ■ | | | | | ■ | | | 32 |
| NK | Res | M | | | | | | | | | | Res | M | | | | ■ | | | | | | 44 |
| MAIT/NKT INNATE LYPHOID CELLS | Res | L | | | | | | | | | | Res | M/L | | | | | | | | | ■ | 42-43 |
| Monocyte activation | Y | M | | ■ | | ■ | | ■ | | | | Res | M | | | ■ | | | ■ | | | | 40.41 |
| Blood dendritic cells | Y | M | | ■ | | ■ | | ■ | | | ■ | Res | M | | | ■ | | | ■ | | | | 41, 52 |
| sCD14 | Y | L | ■ | ■ | | ■ | | ■ | | | | Res | M/L | | | | ■ | | | | | | 46 |
| sCD163 | Y | M | ■ | | ■ | ■ | ■ | ■ | | | ■ | Res/ Limited Long | L | | | | | ■ | | | | | 35, 53 |
| Gut barrier dysfunction (LPS rDNA, IFABP, zonulin Kynurenina/triptofano- KT) | Y | L | ■ | ■ | | ■ | | | | ■ | | Res | M/L | | | | ■ | | ■ | | | | 45 |
| TMAO | Y | M | | | | ■ | | | | | | Target | M | ■ | | | | | | | | | 54 |
| C-reactive protein | Y | H | ■ | | ■ | ■ | ■ | | | | ■ | Clin Ext | H | | | | | ■ | | | ■ | | 55 |
| IL-6 | Y | H | ■ | ■ | | ■ | | ■ | ■ | | ■ | Clin Ext | M | | | | | | | | ■ | | 55-57 |
| D-DIMER | Y | H | ■ | ■ | | ■ | | | | | | Clin Ext | H | | | | | ■ | | | ■ | | 58 |
| ICAM-VCAM | Y | M | | ■ | | ■ | | | | | | Target | M | | | | | | | | ■ | | 59 |
| sCD27 | Y | L | | | | | | | ■ | | ■ | Target | M | | | | | | ■ | | | | 60 |
| sCD40L | Y | L | | | | ■ | | ■ | | | | Target | M | | | | | | ■ | | | | 61 |
| PD-1/antiPD1 | Y | | | | | | | | ■ | ■ | ■ | Target | L | | | | ■ | | ■ | | | | 62-63 |
| TNF system | Y | M | | ■ | ■ | | | | | | | Res | L | | | | | ■ | ■ | | | | 38 |
| IP-10 (CXCL-10) | Y | L | | | | | | | | | ■ | Res | H | | | | | | | | | | 64 |
| MMPs (1, 2, 9) | Y | L | | | ■ | | | ■ | | | | Res | L | | ■ | | | ■ | | | | | 65 |
| IgG CMV | Y | M | | ■ | ■ | ■ | | | | | | Clin Ext/Res | H | ■ | | | | ■ | | | | | 47.48 |
| IFN type 1 | Y | L | | | | | | | | | | Res | M | | ■ | | | ■ | | | | | 37.66 |
| Neopterin | Y | H | ■ | | | | | ■ | | | ■ | Target | H | ■ | | | | | | | ■ | | 67 |
| Beta-2-Microglobuline | Y | H | | ■ | ■ | | | ■ | | | | Target/Res | H | ■ | | | | | | | | | 68 |
| Chemokines (MCP-1/CCL2, MIP-1a/CCL3, MIP-1b/CCL4, RANTES/CCL5) | Y | M/L | | ■ | | | | ■ | | | ■ | Res | M | ■ | | | ■ | | | | | | 69 |

Y = yes; H = high; M = medium; L = low; ■ applies to the item

[75]. However, the association between INI and WG is still controversial.

### 4.4. Bone and vitamin D

PLWHIV have a higher risk for decreased bone mineral density (BMD), low vitamin D levels and fragility fracture than the general population. It is unclear whether HIV infection itself contributes to low BMD; in addition, initiation of ART is associated with a reduction in BMD and vitamin D, which varies with the specific ARV medications used. Osteoporosis and hypovitaminosis D in these patients may be associated with significant long-term morbidity, which is likely to increase as the HIV-infected population ages.

It is appropriate to assess the risk of fragility fracture and low BMD; calculate daily intake of dietary calcium; measure height; assess the 10-year risk of fracture using the Fracture Risk Assessment Tool FRAX score; investigate for specific and reversible secondary causes of osteoporosis or low BMD and assess BMD by DXA scans.

### 4.5. Central nervous system

One of the major current concerns regarding the central nervous system of PLWHIV is the development of HIV-associated neurocognitive disorders (HAND), ultimately affecting patients' overall mortality. Due to its multifactorial pathogenesis, HAND is not completely preventable and even more hardly treatable. Up to 50% of PLWHIV may suffer from this complication, but this estimate is likely inflated by the high false-positive rate of the currently adopted diagnostic Frascati's criteria and alternative criteria are under evaluation.

### 4.6. Gaps and unmet needs

#### 4.6.1. Cardiovascular aspects

The major data gap remains for patients at intermediate risk, that need to be reclassified using adjunctive tools.

#### 4.6.2. Weight gain

Currently, a progressive WG, leading to obesity in some cases, has been observed in PLWHIV receiving ART [75]. For yet unknown reasons, the WG was more pronounced in specific sub-groups of patients, including women and those of African descent. The monitoring of body mass index (BMI), waist and hip circumference appears to be inexpensive and clinically validated tools in order to better evidence the longitudinal changes in body shape [75,76]. Furthermore, body composition can be assessed in PLWH using dual-energy X-ray absorptiometry (DEXA) capable of measuring whole body and regional lean and fat mass [77], but this methodology may not be readily available in most clinical setting.

#### 4.6.3. Bone and vitamin D

The association between $1,25(OH)_2$vitaminD and inflammation found among HIV-infected men suggests a possible mechanism through which inflammation leads to the increased comorbidity risk noted among HIV-infected individuals [78], but this link has to be further investigated.

#### 4.6.4. Central nervous system

Considering that the neurocognitive assessment is time and resource consuming, screening for HAND becomes essential to

limit workload. However, the lack of a diagnostic consensus and the HAND protean clinical phenotype significantly limit our screening possibilities. To date, the only validated screening tools in PLWHIV are the International HIV Dementia scale (IHDS) and the NEU screen, but recent studies demonstrated a poor performance at identifying those HAND subtypes that are now prevailing [79,80].

### 4.7. Perspectives

#### 4.7.1. Cardiovascular aspects

In cases that need to be reclassified about their risk level, the measurement of coronary calcium scores (CAC) has been proposed; however, uncertainty remains about the predictive value of intermediate CAC scores [81].

Echo-color Doppler of carotid vessels is considered a valid prognostic tool. Evidence have shown higher carotid intimal-media thickness (cIMT) in subjects with higher risk or established atherosclerotic disease. Carotid plaque confers a superior diagnostic accuracy for the risk of future myocardial infarction compared to cIMT. cIMT carotid plaques have a significant potential for reclassification in intermediate risk individuals [82].

A vast array of biomarkers has been proposed as candidates for the refinement of risk prediction. C-reactive protein (CRP) is, at present, the only circulating biomarker related to vascular wall biology with a large body of published studies supporting its clinical use for risk stratification [82].

In healthy individuals, systolic BP levels are physiologically higher in the lower extremities as compared to the arms, this relationship can be quantified by the ratio of ankle-to brachial systolic pressure (ABI). A reduction of this ratio heralds a late stage of atherosclerosis [82].

Arterial stiffness results primarily from arteriosclerosis (a disease of the media, related to normal or accelerated aging) rather than from atherosclerosis (a disease of the intima, affecting the vessel in a patchy and not uniform manner). This results in increased velocity of pulse waves. Various invasive and noninvasive methods of measuring arterial stiffness have been described. Carotid- femoral pulse wave velocity (cfPWV) and brachial-ankle PWV (baPWV) are close to being considered a clinical surrogate endpoint or at least fulfill some, but not all of the criteria to be considered as a surrogate endpoint of cardiovascular events. Cardio-ankle vascular index (CAVI) has been recently introduced. CAVI had been correlated with several arteriosclerotic and atherosclerotic diseases [82].

Novel circulating cardiovascular biomarkers have a future potential for prevention, the most promising ones are oxidized low-density lipoprotein and dysfunctional high-density lipoprotein [82].

#### 4.7.2. Weight gain

Leptin has been found to have a profound role in the regulation of whole-body metabolism by stimulating energy expenditure, inhibiting food intake and restoring euglycemia. Adiponectin acts to increase insulin sensitivity, fatty acid oxidation, as well as energy expenditure and reduces the production of glucose by the liver. However, in most cases of obesity leptin resistance limits its biological efficacy and adiponectin secretion can be diminished in obesity [83]. Further studies are needed to evaluate the role of leptin and adiponectin in WG in PLWHIV receiving ART.

### 4.8. Bone and vitamin D

Few data exist on the relevance of bone turnover markers (BTM) in HIV-infected patient management. Following the considerations drawn for the general population it may be suggested that, at least in osteoporotic HIV-patients, BTM can be used both to increase the ability of fracture prediction and to monitor the response to anti-resorptive therapy [84].

Portable quantitative ultrasonometry (QUS) is an alternative technique to provide information about bone density, bone strength, and the BTM in PLWHIV. QUS is easy to use, hence could be used as an alternative to screen HIV patients for altered bone status [85]. Assessment for subclinical vertebral fractures can be done by lateral radiographs of the lumbar and thoracic spine or DEXA-based vertebral fracture assessment [86]. The trabecular bone score (TBS) is a novel index of bone microarchitecture which improves fracture prediction independent of BMD [87]. PLWHIV have lower TBS independently from lumbar spine BMD. Microindentation provides additional and necessary information to DEXA about bone health in treated HIV patients, and because of its convenience and feasibility, it could be routinely applied to assess bone health in clinical practice [88].

### 4.9. Central nervous system

Given the limits of IHDS at identifying currently prevailing HAND subtypes [79,80], several other screening tools are under assessment, such as the Montreal Cognitive Assessment (MoCA) and the Frontal assessment battery (FAB), both borrowed from other neurological disorders 79, 88]. They are all time- and resources-inexpensive, but still in need to prove a reliable diagnostic accuracy. To date, there is not enough evidence to choose one among the others. Combining a few neurocognitive tests selected from the full battery and assessing some of the most commonly affected domains in HAND (motor functions, executive functioning, and memory) could be an alternative to a single full-comprehensive test. Difficulties in reaching a consensus on the diagnostic criteria and on the best neurocognitive battery to be used mainly depends on several gaps that need to be fulfilled. We need a clear description of HAND clinical phenotypes, the identification of what cognitive areas are predominantly impaired, to which extent they are involved and how their involvement changes according to the disease stage. This is justified by the fact that there has been a shift from the subcortical HIV-associated dementias of the pre-cART era to the nowadays-prevailing milder cortical-subcortical forms of HAND. Having a common and thoughtful diagnostic gold standard would subsequently help at identifying the most suitable screening tools. In this regard, specific techniques of brain magnetic resonance imaging,

Table 3. Comorbidities.

| Item | Application in other diseases (Y/N/NA) | Validation status HIV (H/M/L) | Outcomes | Setting (research/clinical extensive/clinical target population) | Feasibility (H/M/L) | Barriers | | | | | | | | Ref (nr) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Cost | Access to specific machines | Time | Lab availability / Availability | False positive/ negative rate | X-dose | Uncertainty about predictive value of intermediate score | Operator-dependant | |
| **CARDIOVASCULAR ASPECTS** | | | | | | | | | | | | | | |
| CAC | Y | M | To reclassify patients at intermediate risk | Clinical extensive | L | ■ | ■ | | | | | ■ | | 73 |
| Echo-color Doppler | Y | M | | Clinical extensive | H | | | | | | | | ■ | 81 |
| CRP | Y | M | | Clinical extensive | H | | | | | ■ | | | | 81 |
| ABI | Y | M | | Clinical extensive | M | | | | | | | | | 81 |
| cfPWV, baPWV, CAVI | Y | M | | Clinical target | M | | | | | | | | | 81 |
| Oxidized low-density lipoprotein, dysfunctional high-density lipoprotein | N | M | To reclassify patients at intermediate risk | Research | L | | | | | | | | | 81 |
| **WEIGHT GAIN** | | | | | | | | | | | | | | |
| Body Mass Index (Kg/m$^2$) | Y | H | WG | Clinical extensive | H | | | | | | | | | 73 |
| Anthropometric measures | Y | H | WG | Clinical extensive | M | | | | | | | | | 74 |
| DEXA | Y | H | Body composition | Clinical target population | M | | ■ | | | | | | | 76 |
| Adiponectin | Y | L | Control of body weight | research | H | | | | | | | | | 82 |
| Leptin | Y | L | Control of body weight | research | H | | | | | | | | | 82 |
| **BONE AND VITAMIN D** | | | | | | | | | | | | | | |
| Assess the risk factors | Y | H | Risk of low BMD | Clinical extensive | H | | | ■ | | | | | | - |
| Daily intake of dietary calcium | Y | H | Osteoporosis risk | Clinical extensive | H | | | ■ | | | | | | - |
| Height | Y | H | Fracture | Clinical extensive | H | | | | | | | | | - |
| FRAX score | Y | M | Fracture risk | Clinical extensive | H | | | ■ | | | | | | - |
| Investigate for secondary causes | Y | H | Osteoporosis/osteomalacia risk | Clinical extensive | H | ■ | | | | | | | | - |
| DXA | Y | H | BMD | Clinical target | M | | | | ■ | | | | | - |
| 1,25$(OH)_2$D | Y | L | Comorbidity risk | Research | M | | | | ■ | | | | | 77 |
| BTM | Y | M | Effect of osteoporosis therapy | Clinical target | M | | | | ■ | | | | | 83 |
| QUS | Y | L | Fracture risk, screening for DXA | Research | L | | | | ■ | | | | | 84 |
| Lateral X-Ray | Y | L | Fracture | Clinical target | M | | | | | | ■ | | | 85 |
| TBS | Y | L | Microarchitecture | Research | L | | | | ■ | | | | | 86 |
| Microindentation | Y | L | Bone quality | Research | L | | | | ■ | | | | | 87 |
| **CENTRAL NERVOUS SYSTEM** | | | | | | | | | | | | | | |
| IHDS | N | H | To detect patients requiring full neurocognitive assessment | Clinical extensive | H | | | | | ■ | | | | 78 |
| FAB | Y | L | | Clinical extensive | H | | | | | | | | | 79 |
| MoCA | Y | L | | Clinical extensive | H | | | | | | | | | 88 |

Y = yes; H = high; M = medium; L = low; applies to the item

such as structural MRI and spectroscopy, will potentially help to better detect HAND, giving objective and quantifiable measures of brain involvement [89], since cerebrospinal fluid biomarkers have not proved to be reliable tools and noninvasive procedures should be preferred. Cerebrospinal fluid levels of Neurofilament Light Protein (NFL) and potentially serum levels, if clinically validated, may provide additional information in the setting of central nervous system and neuronal damage and for diagnosing symptomatic HAND [90].

## 5. Patients reported outcomes

### 5.1. Current status

Patient-reported outcomes (PROs), are defined as any report of the status of the patient's health that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else (e.g. symptoms, functioning, or a more global assessment of the effect of the disease on health and functioning from the patient's perspective).

PRO measures (PROMs) represented the tools to report PROs and are standardized, validated questionnaires that are completed by patients to measure perceptions of health status, level of impairment, disability, and health-related quality of life. They also allow the efficacy of a clinical intervention to be measured from the patients' perspective.

Several questionnaires are widely validated and used, particularly for the measurement of Health-Related Quality of Life (HRQoL). Questionnaire can be generic or disease-specific.

PROs have been used, in different clinical settings, to evaluate the therapeutic benefits of a drug, to support prescriptive indications, to measure the effect of an intervention on quality of life, adherence, symptoms, functional aspect, severity of the disease, treatment satisfaction (Table 4).

Moreover, they can be used in real-world studies such as market research, cost/effectiveness studies and public health research in order to evaluate needs of patients, the acceptability of drugs, the preference of patients according to different drugs, adherence, and correlated factors.

Finally, but they can also be used in clinical practice in order to identify and monitor symptoms reported by the patients and difficulties in taking the treatments.

Given that virologic efficacy levels higher than 85% in patients who starts ART are commonly obtained, there is the need to shift attention from the evaluation of the classic viro-immunologic efficacy toward the measurement of new standards of effectiveness, of which the PROs represent certainly a relevant and innovative aspect.

As reported in several papers [106–116], PROs have been applied to different aspects of the clinical management of HIV infection such as to detect adverse events, to assess the HIV-associated HRQoL in observational studies, and to assess the efficacy of different antiretroviral regimens in comparative trials.

More recently, two double-blind, randomized, phase III studies comparing co-formulated bictegravir, emtricitabine, and tenofovir alafenamide (B/F/TAF) and co-formulated abacavir, dolutegravir, and lamivudine (ABC/DTG/3TC) evaluated changes over time of patient-reported symptoms among HIV-1-infected adults who initiated [117] or switched [118] ART. In both studies, bothersome symptoms were reported by fewer participants on B/F/TAF than those on ABC/DTG/3TC [117,118].

Moreover, PROs have been used to demonstrate the willingness of patients in accepting long acting therapies [119–121] or to show differences between therapeutic strategies as in a sub-analysis of START trial [122].

Table 4. Characteristics of selected PROs instruments organized by main categories of clinical research.

| ITEM | Scale | Validated in non-HIV areas (Y/N/NA) | Validation status HIV (H/M/L) | Mayor strengths | Setting (research/clinical extensive/clinical target population) | Feasibility (H/M/L) | Barriers/Limitations | | | | Ref. (nr) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Culture/population specific | Complex/difficult interpretation | Modest reliability | Not HIV specific | |
| Quality of Life | EQ-5D | Y | H | 1 min completion time for 6 items ( 5 point scale) | Research/clinical | H | ■ | | | | 109 |
| | MOS-HIV Medical Outcomes Study HIV | NA | H | 5-10 mins completion time of 36 items ( 2-6 response for item) | Research/clinical extensive | H | | ■ | | | 110 |
| | MQOL-HIV Multidimensional Quality of Life Questionnaire for HIV/AIDS | NA | H | 10-15 mins completion time of 40 items | Research/clinical | M | ■ | | | | 111 |
| Adherence | (AACTG) Adult AIDS Clinical Trials Group Adherence Baseline Questionnaire II plus modified and adapted versions | NA | H | 10 mins completion time for each questionnaire | Research/clinical | H | ■ | | | | 112 |
| | IRT-10-30 Item Response theory | NA | H | 5 min and 10 min to complete | Research | M | | | ■ | | 113 |
| | SMAQ Simplified medication adherence questionnaire | NA | M | 6-item instrument; <5 min to complete | Research/clinical | M | ■ | | | | 114 |
| Symptoms | HIV-SI | NA | H | 20-item scale, using a 5-point, Likert-type scale; <5 minutes completion time | Research/clinical | H | | ■ | | | 115 |
| | CES-D Center for Epidemiological studies-Depression | Y | H | 20-item instrument on frequency and severity of depression. 15 min time completion | Research/clinical | H | | ■ | | | 116 |
| | PSQI The Pittsburg Sleep Quality Index | Y | M | 19-item instrument 5 minutes completion time. | Research/clinical | H | | | | ■ | 117 |
| Sexuality | IIEF International Index of Erectile function | Y | M | 15-item questionnaire ( 22-item in IIEF-MSM) | Research/clinical | M | ■ | | | | 118 |
| | FSFI Female Sexual Function Index | Y | M | 19-item questionnaire Time to completion: not stated | Research/clinical | M | ■ | | | | 119 |
| | HAT- QoL HIV/AIDS Targeted Quality | NA | M | 42 items based on patient-reported concerns | Research/clinical | M | | | ■ | | 120 |

Y = yes; N = no; NA = not applicable; H = high; M = medium; L = low; applies to the item

### 5.2. Gaps & Unmet needs

Even though the introduction of PROs measurement in clinical practice and clinical research in the HIV setting is widely recommended, some methodological concerns limit, at this moment, their routine use in HIV care. The selection of PROs measures represents the most relevant challenge in clinical practice. Several reviews addressed *the pros* and *cons* of questionnaires on specific domains such as HRQoL and symptoms, but very little is known about other dimensions such as HIV medication beliefs, disability, and no information at all for other relevant aspects of patients' lives such as sexual and reproductive life.

To collect PROs data through touch-screen technology can be feasible, with minimal missing data, high completion rates, modest financial investment and high acceptability by patients, but the implementation process of these tools is far from being applied. Providers themselves are sometimes skeptical about the usefulness of these tools as there is a gap between the collection of PROs and the possibility to intervene afterward to positively impact on PROs themselves. Among the possible explanations of this attitude should be considered the heterogeneity of interventions following PROs measurement, their evaluation methodology, and the jeopardized nature of PROs implementation [123].

### 5.3. Perspectives

In view of the widespread use of ART and the changing face of HIV disease into a chronic condition, over the last few years the impact that such therapies have on many aspects of the life of PLWHIV, often previously undervalued, is becoming increasingly important. Incorporating the patient experience throughout the drug development process is of increasing interest and importance. In order to widely consider the use of PROs in clinical practice, aspects to be addressed include potential barriers and facilitators, either at the level of patients (such as the simplicity of PRO completion), providers (conviction, workload, support and training to use, interpretation), healthcare organizations and interactions between different stakeholders. The implementation of these concepts is pivotal in order to make PROs useful tools for HIV management.

## 6. Conclusions

With the advent of effective ART, steady HIV-RNA suppression has become a usual event and the lifespan of PLWHIV has expanded. The spectrum of diseases experienced by PLWHIV has also changed.

There is a need to consequently assess different ways to measure well-being of our patients.

At present, efforts should be directed, on a case-by-case basis, at preventing virologic failure and favoring optimal recovery of immunity, and also at achieving psycho-physical well-being, which is crucial in the control of a multi-morbidity that needs to be treated for many years.

Each planned intervention has its own specific limitations and often needs dedicated monitoring tools that nowadays must be still refined, for example, many of the proposed markers are only available for research. Further high-level evidence is urgently needed and a concerted multidisciplinary approach is mandatory to understand the meaning of these

new markers that would drive us to get closer to the goal of the fourth 90.

## 7. Expert opinion

Modern ART effectively suppresses HIV-1 RNA load. A 90% virologic success rate is frequently achieved after 48 weeks of ART in clinical trials and the same success rate is reported among chronically treated patients in several different clinical settings, thus meeting the third 90 WHO target.

The way a successful therapy is defined, however, still relies solely on clinical evaluation, HIV-RNA, and CD4 + counts. These factors play a key role in assessing individuals before ART is initiated and then to monitor the response to the treatment and eventual toxicity of antiretroviral drugs.

However, as the potency and efficacy of antiretroviral drugs increases over time and their overall tolerability is nowadays more than satisfactory, the question is if we could rely on two simple measures such as viral load and CD4 counts to define whether a therapy is the best option for an individual patient.

In recent years, research has developed several new markers and ancillary monitoring tools that still have to find their best use in clinical practice.

No specific recommendations are present in guidelines on what the best use of these markers is and how they could contribute to guide clinical practice.

In the context of HIV-RNA suppression, an immediate opportunity that goes beyond the reference 50-copy threshold is the discrimination between target detected (TD) or not detected (TND). The risk of virological failure over time has been correlated to this parameter particularly when the TND status is confirmed across multiple time points. Similarly, HIV DNA extracted from blood lymphocytes or lymphocyte subsets hold promise for profiling the HIV reservoir at an individual level and for supporting patient-tailored treatment strategies.

Theoretically, the combined use of residual HIV replication (e.g. TD/TND) together with other indicators of the HIV reservoir (e.g. HIV DNA) and CAR (cell-associated HIV RNA) should allow to build a full molecular picture of the patient's status and define the more effective ART.

Management of patients with a complex history of drug resistance can benefit from high-resolution NGS that provides a more comprehensive picture of the drug resistance species and may guide treatment choices.

Speaking of lymphocyte activation, raised levels of CD38 + HLA-DR+CD8 + T-cells have a poorer clinical prognostic power than monocyte/macrophage-related inflammation in resource-rich settings while the contrary has been proven in resource-limited settings, where infectious complications still remain a prevalent causes of death.

Pro-inflammatory markers, IL-6, and D-Dimer have shown to be independently associated with non-AIDS co-morbidities and mortality in PLWHIV, suggesting that treatment aiming to decrease these biomarkers may help to reduce morbidity and mortality.

However, because of the wide biological variability of biomarkers and the paucity of interventional studies performed to validate their potential clinical application we are still far from their concrete exploitation in clinical practice.

For co-morbidities evaluation, echo-color Doppler of carotid vessels is considered a valid prognostic tool. Higher carotid intimal-media thickness (cIMT) is present in subjects with higher risk or established atherosclerotic disease. cIMT and carotid plaques have a significant potential for reclassification in intermediate risk individuals.

In osteoporotic HIV-patients, Bone Turnover Markers can be used both to increase the ability of fracture prediction and to monitor the response to anti-resorptive therapy.

Considering that the neurocognitive assessment is time and resource consuming, screening for HAND becomes essential to limit workload. However, we are still far from reaching a consensus on the diagnostic criteria and on the best neurocognitive battery to be used. Several gaps need to be fulfilled. We need a clear description of HAND clinical phenotypes, the identification of what cognitive areas are predominantly impaired, to which extent they are involved and how their involvement changes according to the HIV disease stage.

Body mass index (BMI), waist and hip circumference appear to be inexpensive and clinically validated tools to monitor longitudinal changes in body shape.

The impact that therapies can have on the quality of life of PLWHIV is becoming increasingly important.

The patient experience is, therefore, becoming of paramount relevance both throughout the drug development process and in clinical practice. In order to widely consider the use of PROs in clinical practice, aspects to be addressed include potential barriers and facilitators, either at the level of patients or for providers and other stakeholders.

Certainly, viral load and CD4 counts are well-validated outcome measures and we still need them, but great times and innovative technologies for HIV care are on the horizon, are in development or need validation. It is time to change the pace and to look forward not limiting the choice of ARV therapy on how drugs inhibit the virus, but also as they contribute to obtain the fourth 90 WHO target. Health-related quality of life of PLWHIV must become the center of interest, a goal to constantly pursue and to measure and monitor with reliable tests yet to be completely validated.

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