Pillars of long-term antiretroviral therapy success

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Pillars of long-term antiretroviral therapy success

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ABSTRACT

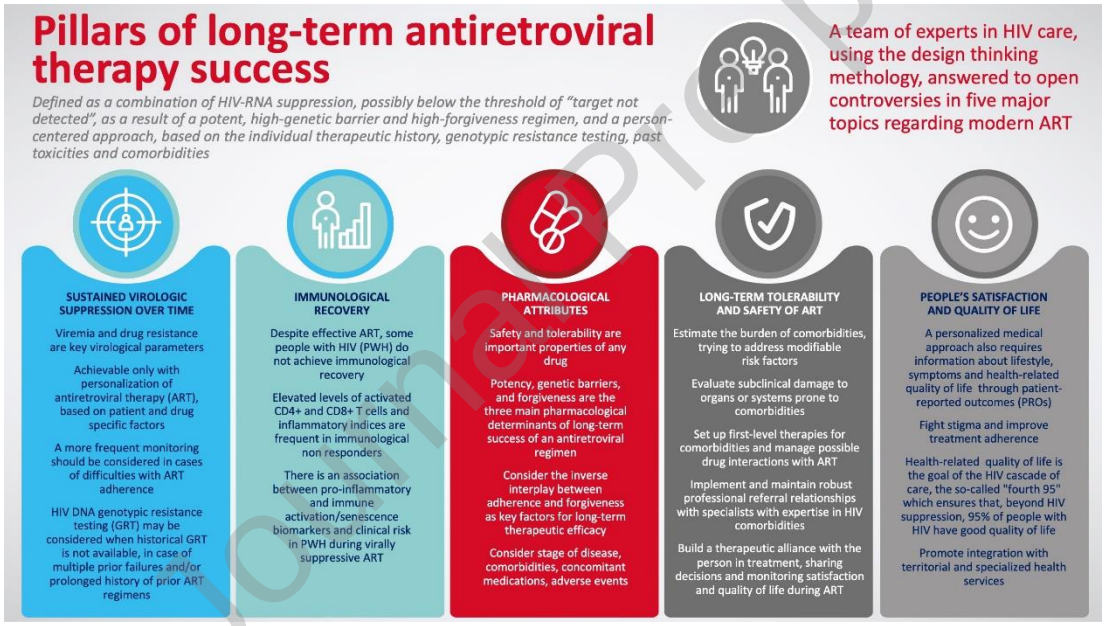
Background. Meeting the challenge of antiretroviral therapy (ART) whose efficacy can last a lifetime requires continuous updating of the virological, pharmacological, and quality of life outcomes to be pursued and a continuous review of literature data on the efficacy and tolerability of new drugs and therapeutic strategies.

Methods. With the aim of identifying open questions and answers about the current controversies in modern ART, we adapted the *Design Thinking* methodology to the needs of the design phase of a scientific article, involving a team of experts in HIV care.

Results. Five main pillars of treatment success were discussed: sustained virologic suppression over time; immunological recovery; pharmacological attributes; long-term tolerability and safety of ART; and people's satisfaction and quality of life. The definition of the outcomes to be achieved in each thematic area and the tools to achieve them were reviewed and discussed.

Conclusions. Long-term treatment success should be intended as a combination of HIV-RNA suppression, immune recovery, and high quality of life. To achieve this, the regimen should be well-tolerated, with high potency, genetic barrier, and forgiveness, and should be tailored by a person-centered perspective, based on individual needs, preferences, and therapeutic history.

Graphical abstract



Keywords: antiretroviral therapy; virologic suppression; immunological recovery; pharmacological attributes; safety; quality of life.

1. Introduction

The modern paradigm of HIV care goes beyond the concept of HIV-RNA plasma viral load suppression and $CD4^{+}$T cell recovery, taking into account also all those factors, pharmacological and

non-pharmacological, general or tailored to the individual, which make the long-term success of antiretroviral therapy (ART) possible. Moreover, the traditional concept of virological suppression has evolved over time, thanks to new evidence on the clinical significance of plasma low-level HIV-RNA and assays with lower thresholds of viral RNA detection that have become widely available in many countries around the world. At the same time, the definition of optimal immunological recovery is still an object of debate, since not only $CD4^{+}$T cell count recovery, but also biomarkers of residual inflammation and immune activation, might be considered. These two pillars of treatment success - viral suppression and immune restoration - should be integrated into a modern vision of therapeutic success with pharmacological attributes of ART, such as potency, forgiveness, and genetic barrier of single drugs and regimens, as well as their long-term tolerability and safety. All of this must be intertwined with the comorbidities of people living with HIV (PWH), which are also related to their aging and increased life expectancy, with the concomitant management of other therapies and drug interactions. Finally, the long-term success of lifelong treatment cannot be separated from the opinions and preferences of PWH, who must be informed, aware, and involved in the choice of treatment to maximize the quality of life, satisfaction, and adherence to ART. In this paper, we identified five major pillars: 1) sustained virologic suppression over time; 2) immunological recovery; 3) pharmacological attributes for long-term success; 4) long-term tolerability and safety of ART; and 5) people's satisfaction and quality of life; on which to base the strategy for achieving long-term therapeutic success. The aim of this paper is to define what the answers are to the open controversies on each topic, according to a team of experts in the different fields addressed by the five thematic areas identified.

2. Methods

2.1. The application of design thinking in the creation of a scientific paper

With the aim of identifying the open questions and answers about the current controversies in five major topics regarding modern ART *(sustained virologic suppression over time; immunological recovery; pharmacological attributes for long-term success; long-term tolerability and safety of ART; people's satisfaction and quality of life),* we used the "Design Thinking" methodology, adapting it to the needs for the design phase of the scientific paper, which led us to greater involvement of people, leading then to greater agility in producing the paper.

2.2. What is Design Thinking

Using a standard definition, Design Thinking is a nonlinear, iterative process that teams use to understand users, challenge assumptions, redefine problems, and create innovative solutions for prototypes and tests. In purely academic terms, Design Thinking is a methodology developed at the Design School of Stanford, USA, in the early 2000s [1]. Usually, the five steps into which the methodology is divided lead the work team from a first phase (Empathize) of analysis and research on the behavior of the end user to the rationalization of the insights collected (Define), to then move on to a more "creative" phase in which the project is shaped (Ideate), until the construction of a first prototype (Prototype) which will then be tested (Test) on a group of end users of the product/service who will provide feedback that can lead to further changes to end up with an almost perfect final product. The backbone of Design Thinking defines which are the steps to follow. Hundreds of tools and toolkits can be used in the various phases that can allow the team that uses it to collect data, process them, create, build a prototype, and then test it.

2.3. The two days of work and the structure of the workshop

We planned our work starting with a two-day workshop. Workshop participants were 32 infectious disease specialists selected for their clinical experience with managing HIV infection, relevant peer-reviewed publications, and active engagement in professional society meetings, who were coordinated by two experts in design thinking. The first day had an introductory function, to make

participants aware of the methodology. The methodology and various steps and toolkits that made it up were presented and explained to participants. The first change to the "conventional path" of Design Thinking was that the first step (Empathize). It is usually intended to find all possible information on the relationship between people (final users) and a specific product or service, but it was replaced by a debate among participants aimed at gathering and delimiting the operational space but also at laying down the conceptual bases of the paper. In practice, the data that are usually collected in the Empathize phase were introduced by the participants themselves, because in this case they were considered custodians of the experience and knowledge that will then flow into the paper.

In the second part of the day, the participants were divided into five groups based on their area of expertise, and each group was entrusted with the development of a functional theme for the final composition of the paper: sustained virologic suppression over time; immunological recovery; pharmacological attributes for long-term success; long-term tolerability and safety of ART; people's satisfaction and quality of life. The task of the groups was to develop the topic on the following day.

The second day of work opened with the phases of Warm Up and Action, that is, those that in the methodology of Design Thinking, correspond to the phases of Define and Ideate. The groups summarized and schematized their thinking on a large blackboard, visually composing their theses and the content of the paper itself. In this phase, each paper support inserted in the blackboard, each scheme, and each formula, led to further debate and in-depth analysis among the members of the groups, facilitating them in having a global vision of the theme entrusted to them.

Subsequently, a representative of each group exposed to the other working groups what had been elaborated, in order to be able to collect feedback and critically discuss the various topics. This phase has been renamed Contamination, as it was intended to create synergies among the working groups and the topics covered, in order to develop links and give life to further areas of deepening. Making a comparison with the original five key points of Design Thinking, in this phase the first prototype of the paper was drawn and passed under the scrutiny of the other working groups and scientific reviewer committee members, becoming the testing phase of the paper itself. Once the feedback from the

participants was collected, the materials on the blackboard were refined. The five topics: Sustained virologic suppression over time; Immunological recovery; Pharmacological attributes for long-term success; Long-term tolerability and safety of ART; People's satisfaction and quality of life, are presented in chapters 3-7 of the present paper

3. **Sustained virologic suppression over time**

3.1. Sustained virological response: definition and clinical significance

HIV virological suppression is defined as a plasma HIV RNA load below the lower level of detection, as measured by highly sensitive assays with lower limits of quantitation ranging from 20 to 75 copies/mL [2]. The European AIDS Clinical Society (EACS) guidelines provide a strong level of recommendation to achieve this goal [3]. Considering different cut-offs, the threshold of the target not detected (TND) is the safest for preventing virologic failure or rebound, while to prevent sexual transmission, a value of ≤200 copies/mL is necessary (undetectable equals untransmittable, that is, U=U) [4,5]. The clinical consequences of maintaining virological suppression are at the personal and community levels. At the first level, it favors maintenance of $CD4^+$ and $CD8^+$ T cell balance, low level of systemic inflammation, and prevention of drug resistance development. At the community level, the benefits include prevention of the spread of HIV infection, contributing to achieve the target of "zero level" of new HIV infections by 2030.

The European guidelines underline the need for preparedness of PWH to achieve this goal; in particular, the need for lifelong treatment requires the willingness of the person to adhere perfectly to the regimen [3]. Infectious disease physicians should use appropriate techniques to assist all PWH in starting ART and achieving and maintaining virological suppression. Sustained virologic success requires the engagement of people in treatment and eventually the re-engagement of those who were lost to follow-up (LTFU). Re-engagement in care of those people who stopped ART is a difficult but pivotal process, and sometimes unsuccessful, despite all efforts [6]. Database searches,

phone calls, and/or mail contacts were the most common strategies used to locate and track LTFU, while motivational interviews and strength-based techniques were used most often during re-engagement visits [7].

3.2. Virological failure: definition and clinical significance

Virological failure is usually defined as a confirmed HIV-RNA viral load (VL) >50 copies/mL in PWH with previously undetectable VL (virological rebound) or at 6 months after initiation of therapy in a person not previously treated with ART (incomplete suppression). In people with very high baseline VL (>100,000 copies/mL), achieving viral suppression may take more than six months [3]. However, the definitions of optimal viral suppression vary considerably between studies and clinical guidelines [2]. Several studies support the hypothesis that virologic failure is more likely to occur in patients with a viral load ≥200 copies/mL than in those with low-level viremia between 50 and 199 copies/mL. However, other studies have suggested that viremia detectable at this low (<200 copies/mL) or even lower (<50 copies/mL) levels may be predictive of virologic failure and may be associated with the evolution of drug resistance [2,8]. In cases where VL >50 and <200 copies/mL, guidelines recommend checking for adherence and reinforcing it, checking VL one to two months later, and if genotyping shows no resistance mutations, maintaining current ART if it contains either integrase strand transfer inhibitors (INSTI) with a high genetic barrier to resistance such as bictegravir (BIC) or dolutegravir (DTG), or boosted protease inhibitors (PI/b), otherwise monitoring carefully [2,9].

3.3. Residual viremia and viral blips: definition and clinical significance

Residual viremia is defined as a detectable HIV RNA load of <50 copies/mL. The possibility of accurately quantifying residual viremia depends on the assay used. The most commonly used commercial assays running on fully automated platform can only indicate qualitative detection below the lower limit of quantification (20 HIV-RNA copies/mL in the most sensitive systems). Some research use assays, particularly those based on the digital droplet PCR (ddPCR) technique

are more accurate with values <20 HIV-RNA copies/mL although the bottleneck limiting the threshold of sensitivity ultimately remains the volume of blood processed, which can hardly be increased in the clinical setting. Although the clinical significance of residual viremia is still debated [10], its detection has been associated with a higher risk of subsequent virological failure [11,12]. The level of risk is low, and the available evidence does not support intensifying treatment by adding new drugs in order to modify the burden of residual viremia [13]. However, residual viremia is associated with a higher level of inflammation, which can result in an increased risk of cardiovascular events [14], although not all studies agree [15]. Viral blips are usually defined as unconfirmed HIV-RNA >50 copies/mL, that is, the detection of a single plasma HIV-RNA >50 copies/mL, preceded and followed by HIV-RNA values <50 copies/mL. Viral blips have not been consistently associated with a significant risk of virological failure or selection of drug-resistant HIV variants. Thus, guidelines do not recommend changing the ongoing regimen when viral blips occur. Nevertheless, it makes sense for closer viral load monitoring in the months following the detection of a viral blip to evaluate the frequency of these episodes [16].

3.4. Virological parameters required for the maintenance of a sustained virological suppression

In the management of HIV infection, viremia, and drug resistance remain the key virological parameters to be considered to guarantee a sustained virological response [2,3]. For people on ART, VL typically needs to be measured every 3–6 months. More frequent monitoring should be considered in cases of difficulties with ART adherence, while adherent PWH with consistently suppressed viral load and stable immunologic status for at least two years, monitoring can be extended to 6-month intervals [2,3]. A cumulative genotypic resistance history should be considered together with a complete history of ART and viremia in virologically suppressed people or in those with low viremia levels (<200 copies/mL) for whom a therapy switch is planned [2,3]. In these PWH, the standard genotypic resistance test (GRT) of plasma virus is not possible, while resistance GRT performed on peripheral blood mononuclear cells (PBMCs) is technically feasible [17,18]. Therefore, HIV DNA

GRT may also be considered, particularly for PWH who have experienced multiple prior failures, a prolonged history of prior ART regimens, and/or unavailable resistance history. However, this assay may not detect previous resistance mutations and can also detect clinically irrelevant mutations; thus, the results should be interpreted with caution. Few studies have demonstrated the clinical relevance of drug resistance mutations detected by PBMC GRT [17] and thus routine PBMC GRT is currently not recommended [2,3]. Another aspect to consider is the evolution of the genotyping procedures. GRT through bulk sequencing has long been effective in supporting ART. However, Sanger sequencing can only detect the presence of mutations occurring in at least 20% of the viral population. The detection of lower-abundance drug-resistance mutations (with a prevalence of up to 0.1%) is now possible through Next Generation Sequencing (NGS) approaches [19,20]. So far, most clinical applications of NGS have used thresholds between 5 and 10%, however further studies are needed to evaluate the most clinically relevant threshold for NGS.

3.5. Strategies for maintaining virologic suppression

Personalization of ART is the first strategy for maintaining virological suppression. This requires a shared decision-making process between the patient and physician, considering patient preferences, pill burden, potential adverse effects and costs. The personalized approach involves selecting the optimal treatment regimen based on patient-specific factors, including age, comorbidities, concomitant medications, adherence difficulties, and preferences [21]. The increasing burden of comorbidities, related to the aging of PWH, asks for both observational studies and clinical trials to investigate whether different ART strategies might influence the virological outcome in PWH with comorbidities or in the elderly population, also considering the interplay between clinical disease progression and ART [22,23]. All potential pharmacokinetic interactions between ART and other concomitant medications should also be assessed before prescription and PWH should be counselled about the risks of drug interactions at each clinic visit. A full medication history,

including herbal medicines, recreational drugs and other non-prescribed medications, should be taken at least annually [24].

4.Immunological recovery

4.1. Immunological recovery in treated HIV infection

HIV infection is characterized by complex alterations in the immune response involving both humoral and cellular compartments [25], with possible quantitative damage (lymphopenia, with a prevalent reduction in $CD4^+$T cells and variable CD8+ deficiency), but also functional alterations. Impaired T-cell proliferative responses to specific mitogens and antigens, decreased cellular mediated immunity (CMI) to opportunistic agents, poor control of B lymphocyte responses, impairment of chemotaxis and natural killer activity are among the best-known alterations in people who develop AIDS [26]. The introduction of ART allows the recovery of $CD4^+$T cell numbers, resulting in reduced AIDS-related morbidity and mortality. However, the degree of immune recovery in PWH undergoing effective ART, usually measured in terms of peripheral blood $CD4^+$T cells variation, is not yet fully understood. Approximately 20% of PWH, known as immunologic-non-responders (INRs), have difficulty recovering this $CD4^+$T cell count [27], and there is considerable variability in the extent of immune functional restoration in treated individuals. Functional studies on CMI towards specific antigens (e.g. Cytomegalovirus, Mycobacteria) seem to correlate the numerical with the functional recovery of $CD4^+$T cells, but this does not happen in all PWH, as some develop opportunistic disease despite a normal $CD4^+$T cell count [28,29]. As an additional measure of immune impairment, some PWH, especially those with advanced disease, have a suboptimal humoral response to vaccines [30]. Moreover, even in chronically treated PWH, it is not uncommon to find elevated levels of activated $CD4^+$ and $CD8^+$ T cells and inflammatory indices (IL-6, D-dimer, C-reactive protein, and soluble CD14), clear signs of immune activation that persists despite therapy [31].

4.2. Biomarkers of immune recovery and evidence for their use in clinical practice.

Although defective immune recovery in PWH under fully suppressive ART has been ascribed to several immunologic pathways, it is most likely a multifactorial phenomenon [32]. Impaired T-lymphocyte neo-synthesis has been associated with scant immune recovery in ART, involving both bone marrow and thymus dysfunction. Indeed, the bone marrow of INRs features altered clonogenic capacity and stromal cell function [33], fewer functional precursors, and reduced Interleukin-7 (IL-7)-IL-7R production [34]. Likewise, a constrain in both thymic size as assessed by radiologic imaging [35] and in thymic function, measured through extensive T-lymphocyte immunophenotyping and T-cell receptor excision circles (TRECs) quantitation in peripheral blood [36–38] have been shown to correlate with the degree of $CD4^+$T cell recovery upon ART initiation and throughout long-term effective therapy. Along with reduced T-lymphocyte neo-synthesis and peripheral homeostasis, PWH lacking a satisfactory $CD4^+$T cell gain also maintain a hyperactivated and hyper-inflamed immune asset despite fully suppressing HIV replication [39–42], with the accumulation of senescent, pro-apoptotic T-lymphocytes [43,44], as well as several pro-inflammatory soluble markers. Such a hyper-activated and exhausted immune profile has been demonstrated to occur both in peripheral blood and lymphoid organs [45,46]. Inflammation within lymphoid organs leads to collagen deposition and tissue fibrosis [47], which in turn further exacerbate immune dysfunction. The alterations in the gastrointestinal system deserve specific attention. By hosting about 70% of the T-lymphocyte pool, the gut is a major site of HIV pathogenesis, with structural and functional damage occurring since the earliest stages of the infection, that consists in the loss of mucosal intercellular junctions and mucosal-associated T-cell subtypes [48], leading to the continuous passage of microbial byproducts from the intestinal lumen to the systemic circulation (microbial translocation) [49–51]. Circulating microbial products are themselves potent pro-inflammatory stimuli that significantly contribute to maintaining inflammation in ART-treated PWH [34]. Indeed, the ex vivo stimulation of PBMCs from treated PWH with several microbial challenges such as lipopolysaccharide (LPS), lipoteichoic acid (LTA),

Peptidoglycan (PGN), ssRNA leads to the increased expression of activation and pro-apoptotic markers on T-lymphocytes, as well as production of soluble markers, with differences according to the extent of the $CD4^+$T cell recovery, therefore providing a proof of the effect of systemic exposure to microbial agents as driver of immune activation during ART through toll like receptor (TLR) engagement [52]. Irrespective of the mechanism(s) of immune dysfunction, INRs are at increased risk of disease progression, both through AIDS and non-AIDS-related events [53], supporting the use of biomarkers indicative of immune deficit and immune activation/inflammation as surrogate indicators of clinical risk.

Many cohort studies as well as nested analyses within large clinical trials have convincingly demonstrated an association between pro-inflammatory and immune activation/senescence biomarkers and clinical risk in PWH during virally suppressive ART (Table 1). However, such biomarkers are known to significantly fluctuate both inter- and intra-individually and are influenced by several co-factors such as concurrent acute or chronic co-infections, as well as other physiological and pathological processes.

The high biomarker variability together with the cost and poor feasibility of assessment in routine settings, combined with the lack of validated therapeutic interventions, have altogether substantially restrained the rationale for their exploitation in the clinical management of PWH. However, understanding the different patterns of inflammation, immune activation, and senescence that may exist during different stages of HIV infection could be crucial to developing personalized therapeutic strategies for long-term success in the future. A possible, simple surrogate marker to overcome the above-mentioned limitations of immune biomarkers, that might successfully estimate residual immune dysfunction and inflammation in PWH on ART is the $CD4^+/CD8^+$ T cell (CD4/CD8) ratio.

4.3. Use of $CD4^+$T cell count and CD4/CD8 ratio as markers of immunological recovery

The $CD4^+$T cell count is currently considered the key immunological prognostic marker since it has a strong inverse correlation with the risk of disease progression towards AIDS-defining conditions, non-AIDS-defining conditions, and death [54,55]**.** However, people with equivalent $CD4^+$T cell counts may have diverse functional immune characteristics and residual inflammation [56]. The assessment of the CD4/CD8 ratio can add important information, as it is a marker of immune-senescence, immune-activation, and inflammation [53,57–61], and is less influenced by total white blood cell variability than the absolute $CD4^+$T cell count. A low CD4/CD8 ratio could be interpreted as an epiphenomenon of dysregulation and immunological activation of the immune system with hyperinflammation and immuno-senescence [62] and has been associated with non-AIDS-defining events, mortality, and premature aging also in PWH with virological control and $CD4^+$T cell reconstitution [58]. Moreover, its evaluation at first clinical presentation is a strong predictor of future immunological recovery [63–65] and it has been found to be lower after 36 months of ART in INRs than in full responders, supporting the hypothesis that persistent immune activation impairs reconstitution of the immune system and $CD4^+$T cell gains in INRs [40,65]. Although its correlation with non-AIDS deaths is not confirmed in all studies [66], given the wide availability of data in support of its correlation with important clinical outcomes, the possibility to determine it more easily and less expensively than other soluble and cellular markers, it remains, to date, the most widely used marker of a patient's immune dysregulation and inflammatory status.

Clinical Outcome	**Study Design and Population Number**	**Marker(s) Studied**	**Study Findings**	**Reference**
AE/SNAEs/mortality	Cohort study on 486 ART-naïve subjects with 125 clinical events	LPS, sCD14, EndoCab, hs-CRP	hs-CRP was the only predictor of clinical progression	Merlini, BMC Infectious

				Diseases, 2021[67]
Mortality	477 of 485 subjects randomized to defer ART in the TEMPRANO trial	IL-1ra, IL-6, sVCAM-1, sCD14, D-dimer, fibrinogen, IP-10, sCD163, albumin, hs-CRP, 16S rDNA	pre-ART plasma sVCAM-1 and sCD14 levels independently associated with mortality	Affi, JAIDS, 2021 [68]
Mortality	606 HIV-infected women	T-cell markers: CD38, HLA-DR, CD57, CD28, PD-1	CD4+HLA-DR+CD38+ and CD4+PD-1+ associated with risk of natural-cause and non-HIV-related mortality	Peters, JID, 2021 [69]
SNAEs	Nested case-control study from the ACTG ALLRT cohort. Subjects were evaluated i) pre-cART (66 cases, 97 controls); ii) 1 year post-cART	T-cell markers: CD27, CD28, CD40, CD80, CD86,	CD27 associated with increased risk of SNAEs events at all time points	Premeaux, OFID, 2022 [70]

	(112 cases, 211 controls), and preceding a SNAE (89 cases, 162 controls)	GITR, GITRL, HVEM, BTLA, ICOS, CTLA-4, LAG-3), PD-1, PD-L1, TIM-3		
SNAEs	See above	Galectin-9	Galectin-9 associated with increased risk of sNAEs at year 1 and pre-event	Premeaux, AIDS, 2021 [71]
SNAEs/mortality	Cross-sectional study on 3756 ART-treated subjects included in SMART (n= 1748), ESPRIT (n=1446), SILCAAT (n=572)	IL-6, D-dimer, hs-CRP	IL-6 and D-dimer independently associated with SNAEs or death	Grund, PLoS One, 2016 [72]
SNAEs	Longitudinal study on 249 ART-treated subjects	IL-6, D-dimer	Pre-seroconversion D-dimer levels associated with an increased risk SNAES	Freiberg, PLoS One 2016 [73]

SNAEs	Case (SNAE, n=39)-control (no SNAEs, n=39); markers measured at enrollment and pre-event	sCD14, sCD163, IL-6	Unchanged/slow decrease of sCD14 and IL-6 predict SNAEs	Sunil, AIDS Res and Hum Retrov, 2016 [74]
SNAEs/mortality	Case (SNAE or death, n=143)-control (n=315); markers measured pre-cART, 1 year after cART and pre-event	IL-6, IFN-γ, sCD14, IP-10, sTNFR-I, sTNFR-II, KT ratio, D-dimer; T-cell markers: CD38, HLA-DR, PD1, CD57, CD28	IL-6, sTNFR-I/II, plasma KT ratio, D-dimer at 1 year associated with SNAE	Tenorio, JID, 2014 [75]
Mortality	Case (LSOCA, n=64+SCOPE, n=27) control (LSOCA, n=128+SCOPE, n=54) study on cART-treated subjects with undetectable viral load	IL-6, I-FABP, sCD14, hs-CRP, zonulin-1, sTNFR-I, D-dimer, KT ratio; T-cell markers:	I-FABP and zonulin-1 were strong predictors of death in individuals with a history of AIDS	Hunt, JID, 2014 [76]

		CD38/HLA-DR, PD1, CD31, CD57/CD28, CD27, CCR5, CCR7, CD45RA		
Cardiovascular disease	672 subjects on ART	CMV IgG titre	CMV Ig titre not associated with coronary artery disease indexes	Schnittman, CID, 2022 [77]
Cardiovascular disease	398 women (73% HIV+) and 339 men (68% HIV+) without carotid artery plaques at baseline	Plasma levels of C16:0, C22:0, C24:0, C24:1 ceramides	Higher C16:0 and C24:1 significantly associated with increased risk of carotid artery plaques	Zhao, Circulation, 2022 [78]
Cardiovascular disease	43 HIV-infected individuals on ART	T-cell markers: PD-1, TIGIT, TIM-3	Higher frequency of PD-1+, TIGIT+, and dual PD-1+ TIGIT+-expressing CD4+ T cells and	Bowler, JAIDS, 2019 [79]

			progression of coronary calcium	
Cardiovascular disease	149 HIV-infected individuals on ART	IL-6, hs-CRP, sCD14, sCD163, D-dimer, sTF; T-cell markers: HLA-DR, CD38, CD57,CD28; monocyte markers: CCR2, CX3CR1, CCR5)	Higher monocyte CCR5 expression and plasma IL-6 were associated with atherosclerosis	Hsu DC, AIDS 2016 [80]
Cardiovascular disease	Cross-sectional study on 575 HIV-infected men (242 cART-treated) and 348 healthy controls	IL-6, sICAM-1, fibrinogen, d-dimer, hs-CRP, sTNFR I and II	Higher inflammatory marker levels associated with greater prevalence of coronary stenosis	Bahrami H, J Am Heart Assoc, 2016 [81]
Cardiovascular disease	252 HIV-infected individuals (225 ART-treated, 27 ART-naïve)	IL-6, cystatin C, hs-CRP, TNF-α, D-dimer	Higher number of elevated biomarkers associated with a higher	Mooney S, PLoS One 2015 [82]

			mean VACS and Framingham scores	
Cardiovascular disease	Cross-sectional study on 147 ART-treated HIV-infected individuals	sCD14, sCD163, hs-CRP, IL-6, sTNFR-II, sVCAM-1, OPG, RANKL	sCD14 independently associated with coronary artery calcification	Longenecker CT, AIDS 2014 [83]
Cardiovascular disease	Cross sectional study on 61 ART-treated HIV-infected individuals	LPS, sCD14. hs-CRP, D-dimer, ADMA, SDMA	sCD14 is associated endovascular dysfunction	Pedersen KK, JAIDS 2014 [84]
Cardiovascular and Bone disease	Cross-sectional study on 94 ART-treated HIV-infected individuals and 41 uninfected controls	OPG; T-cell markers: HLA-DR, CD38, CD57, CD28	Higher T-cell activation/senescence and OPG in subjects with pathological c-IMT and BMD	D'abramo A, PLoS One 2016 [85]
Bone disease	Prospective, matched cohort study on 47 ART-naive HIV-infected individuals and 41 uninfected controls	sVCAM-1, sICAM-1, IL-6, sTNFR I and II, hs-CRP, vitamin D	Higher serum IL-6 concentrations associated with progression to osteopenia/osteoporosis status HIV	Hileman CO, AIDS 2014 [86]

Bone disease	Cross-sectional 142 ART-treated HIV-infected individuals	RANKL, OPG, sVCAM-1, sICAM-1, IL-6, TNF-α, sTNFR I and II, hs-CRP, D-dimer, sCD14, sCD163	Bone health correlated with sVCAM-1 and sICAM-1	Erlandson KM, JAIDS 2014 [87]
Central Nervous System disease	Cross-sectional study on 76 HIV-infected women grouped by cognitive performance and 38 controls uninfected controls	sIR in plasma and urine; sIR, HIV-1 Tat, and ROS in exosomes	iHIV-infected women with symptomatic cognitive impairment presented higher plasma sIR as well as exosome levels of sIR and ROS.	Cantres-Rosario, Front Neurol, 2022 [88]
Central Nervous System disease	Longitudinal study (pre- and post-ART) on 51 acutely-infected HIV individuals	sCD163	In Fiebig stage III, higher sCD163 levels pre- and post-cART in Fiebig stage III correlated with poor CNS measures; in Fiebig stage I/II pre-cART, this association was linked with	D'Antoni ML, JID 2018 [89]

			favorable CNS outcomes.	
Central Nervous System disease	Cross-sectional study on 90 ART-treated HIV-infected individuals and 94 uninfected controls	D-dimer, IL-6, MCP-1, sCD14, TNF-α	Worse complex motor performance and higher average inflammation burden composite score in HIV-infected individuals	Montoya JL, JAIDS 2018 [90]
Central Nervous System disease	Cross-sectional study on 41 ART-treated HIV-infected individuals	mtDNA, sCD14, TNF-α, IL-6, IL-8, MCP-1, IP-10, NFL	mtDNA in the CSF significantly correlated with MCP-1 in the same compartment as well as TNF-α and IL-8 in plasma	Perez-Santiago J, JNV 2017 [91]
Central Nervous System disease	Longitudinal study on 99 ART-treated, HIV-infected individuals grouped by cognitive performance	Neopterin, NFL	Higher CSF neopterin in the group with cognitive impairment; NFL and neopterin were significantly correlated within the same group	Edén A, PLoS One 2016 [92]
Central Nervous System disease	Cross-sectional study on 67 people with HIV (55 ART-treated, 12 ART-naive)	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13,	CSF sCD14 associated with impaired neurocognitive testing in non-suppressive	Kamat A, JAIDS 2012 [93]

		IL-17, IFN-α, IFNγ, TNF, GM-CSF, MCP-1, MIP-1α, MIP-1β, IP-10, MIG, eotaxin, RANTES sCD14	ART-treated individuals; CSF sCD14, IL-6, IL-8, MCP-1, MIP-1 α, IP-10, and IFN-γ remain elevated in suppressive cART-treated individuals regardless of cognitive status	

Table 1. Biomarkers of immune recovery and evidence for their exploitation in literature.

AE: AIDS (Acquired Immune-Deficieny Syndrome) Event; SNAE, Serious Non AIDS Event; ART,Antiretroviral Therapy; LPS, Lipopolysaccharide; sCD14, soluble CD14; EndocAb, Endotoxin-core Antibodies; hsCRP, high-sensitivity C Reactive Protein; IL, Interleukin; IL-1ra, IL-1 receptor antagonist; sVCAM-1, soluble Vascular Cell Adhesion Molecule-1; GITR/L, glucocorticoid-induced TNFR-related protein/ligand; HVEM, herpesvirus entry mediator; BTLA, B- and T-lymphocyte attenuator; ICOS, inducible T-cell co-stimulator; CTLA-4, cytotoxin T-lymphocyte-associated protein 4; LAG-3, lymphocyte-activation gene 3; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1 (PD-L1) ; TIM-3, T-cell immunoglobulin and mucin-domain containing 3; sCD163, soluble CD163; IFN- γ, interferon-γ; IP-10: IFN-γ -inducible protein 10; sTNFR-I/II: soluble Tumor Necrosis Factor Receptor I/II; KT, kynurenine -to- tryptophan; LSOCA, Longitudinal Study of the Ocular Complications of AIDS; SCOPE, Observational Study of the Consequences of the Protease Inhibitor Era; I-FABP, Intestinal Fatty Acid Binding Protein; CMV, cytomegalovirus; TIGIT, T-cell immunoreceptor with Ig and ITIM domains; sTF, soluble tissue factor; sICAM-1, soluble Intracellular Adhesion Molecule 2; TNF-α, Tumor Necrosis Factor-α; VACS, Veterans Aging Cohort Study; OPG, osteoprotegerin; RANKL, Receptor Activator of Nuclear Factor Kappa-B Ligand; ADMA, asymmetric dimethylarginine; SDMA, symmetric dimethylarginine; c-IMT, carotid-Intima Media Thickness; BMD, Bone Mineral Density; sIR, soluble Insulin Receptor; ROS, Reactive

Oxygen Species; MCP-1, Monocyte Chemoattractant Protein-1; mtDNA, mitochondrial DNA; NFL, neurofilament (light chain); CSF, cerebrospinal fluid; MIP-1 α/β, Macrophage Inflammatory Protein-1 α/β; GM-CSF, Granulocyte-macrophage colony-stimulating factor; MIG, Monokine Induced by Gamma Interferon.

5.Pharmacological attributes for long-term success

5.1. Pharmacologic determinants of long-term treatment success

The dramatic change in the natural history of HIV infection since the advent of ART has redefined long-term ART success according to five main concepts: efficacy, safety, rapid initiation, simplicity, and quality of life [94]. In addition to being the core of adherence to treatment, safety and tolerability are the most important properties of any drug, since they design the therapeutic range. Once safe doses have been established, the efficacy of ART relies on the activity of the individual antiretrovirals in the regimen, that is the potency of the regimen, and on the number of genotypic resistance mutations required for the development of resistance, otherwise called the genetic barrier [95]. At least one drug with a high genetic barrier should be included in ART regimens. The ideal regimen should include molecules with similar profiles, preferably characterized by a high volume of distribution, to reach the sanctuaries of viral replication, and by a long terminal half-life, the time required to divide the plasma concentration by two after reaching pseudo-equilibrium [96], which allows, on one hand, lower doses per day, once daily in the best cases, and on the other hand, a persistent inhibitory efficacy even in the case of missed doses and thus a high forgiveness [97,98]. To date, low adherence to ART is a major determinant of virologic failure [99] highlighting the importance of forgiveness.

5.2. Role of pharmacological determinants at different stages of therapy

Potency, genetic barriers, and forgiveness of the regimen are the three main pharmacological determinants of long-term success (Figure 1A). An ideal therapy should combine the maximum

expression of these determinants into a single combination, however, the role of each can be different in the different stages of ART (Figure 1B). In a person naive to ART, is an attack phase of therapy, the goal of rapid HIV RNA suppression requires the maximal potency of ART, while the genetic barrier of the regimen is important to prevent the selection of resistance mutants before virologic suppression is achieved [100]. After obtaining HIV RNA undetectability, the goal of therapy is to maintain this ideal situation, and the tolerability and forgiveness of the treatment become crucial, and more critical than the potency of the regimen, over the long term [101–103]. Suboptimal adherence to drugs is relatively common and can increase over time, therefore forgiveness, defined as the ability to maintain an antiviral effect even after the dosing interval, is crucial [101–103]. Regimen forgiveness is a function of plasmatic and intracellular half-lives of different compounds [102,103]. The use of a backbone based on two drugs supports forgiveness, as in the case of TDF/TAF and FTC, the two antiretroviral drugs with longer intracellular half-lives. In the clinical setting, for example, BIC/FTC/TAF was shown to have more prolonged forgiveness than the dual regimen 3TC/DTG: the minimum requested adherence to maintain virological efficacy was 90% for 3TC/DTG and 70% for BIC/FTC/TAF [102,103]. These findings suggest an inverse interplay between adherence and forgiveness as key factors for long-term therapeutic efficacy: the higher the adherence, the lower the request in terms of forgiveness. In addition, in the maintenance phase, the role of the genetic barrier remains key, preventing the loss of efficacy of the regimen in case of resumption of viral replication.

The recent availability of cabotegravir and rilpivirine as injectable long-acting compounds could change the scenario. Forgiveness and adherence are no longer factors to be considered if assuming correct compliance to all injections (Figure 1B). However, along with the genetic barrier, the pharmacological determinant that replaces forgiveness is here an adequate PK exposure (Figure 1B). When present along with at least one other risk factor, BMI over 30 (which implies injection in adipose tissue and very slow release of drugs) and low rilpivirine PK are known risk factors for virological failure in this maintenance therapeutic strategy [104,105]. Moreover, long-acting formulations of cabotegravir and rilpivirine, with intramuscular administration, have different

elimination half-life of, respectively, 5.6-11.5 weeks and 13-28 weeks [106]. This implies the possibility of exposure to rilpivirine alone after the elimination of cabotegravir, in case of treatment withdrawal, when people are lost to follow up or refuse a new treatment initiation, with consequent risk of emergent mutations to rilpivirine. Also, mutations to rilpivirine and/or integrase inhibitors have been reported in the rare cases of virological failure reported in the SOLAR switch trial, while no cases of virological failure was reported in the comparator arm with BIC/FTC/TAF [107].

From this viewpoint, increasing experience in the clinical setting will help to better define the possible weaknesses of each strategy. These general principles should be considered when selecting treatment regimens, combining them with the evaluation of the long-term possible drug toxicities and the person's needs and preferences, which remains imperative for the goal of long-term success.

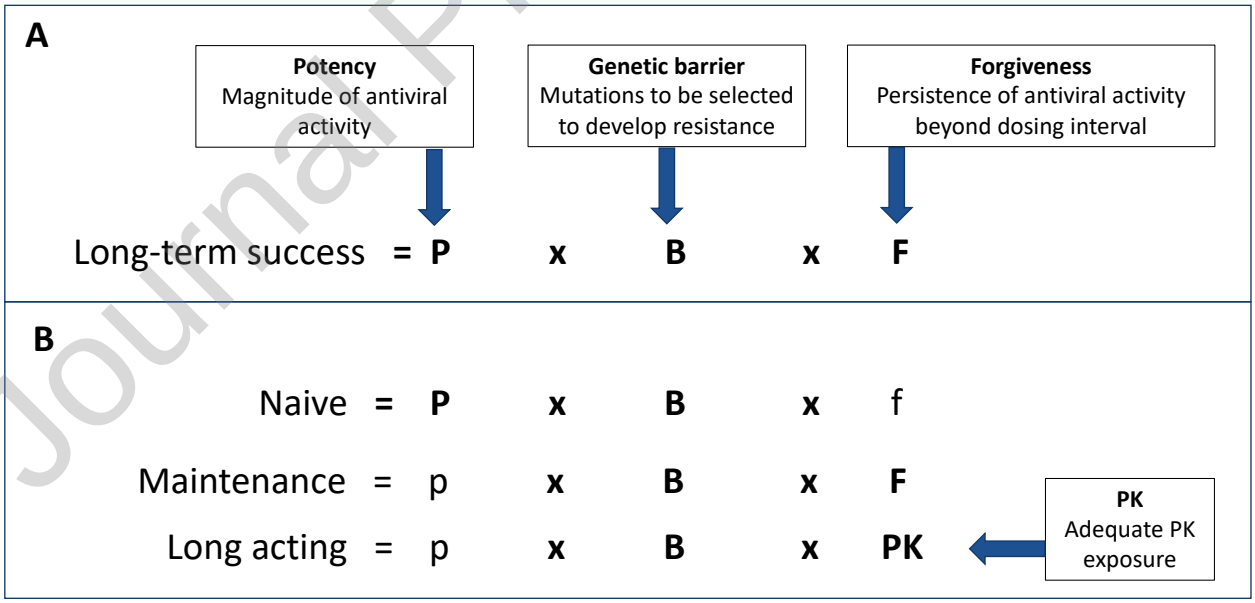


Figure 1. Long-term virological success– Pharmacological determinants. *Potency, genetic barriers, and forgiveness* of the regimen are the three main pharmacological determinants of long-term success (1A). The role of each determinant changes in the different stages of the therapy (1B).

B: genetic barrier; F: forgiveness; P: potency; PK: pharmacokinetics. Abbreviations are shown in the figure with capital letters where the determinant indicated by the abbreviation has a greater weight, and with lowercase letters where the weight of the same determinant is lower.

5.3. Pharmacological considerations tailored to the person

As discussed in the previous section, the pharmacological attributes of therapy should be tailored according to the needs of the individual to achieve therapeutic success. In particular, one should consider:

a) Stage of disease: a late HIV diagnosis with concomitant opportunistic events, implies the use of a regimen with low drug interactions, possibly not including pharmacokinetic enhancers, to allow treatment of opportunistic events without potential drug–drug interactions (pDDIs), if safe and effective options are available [2].

b) Comorbidities: despite ART efficacy, a set of HIV-associated complications persist, which are related in part to the premature ageing observed in some PWH. Indeed, treatment does not seem to fully recover from increased inflammation and restore immune health and the appearance of complications such as cardiovascular disease and cancer has not decreased

accordingly. Some chronic diseases, including stroke, lung diseases, diabetes, cardiovascular diseases, hypertension, cancers and neurocognitive disorders, can occur more often in PWH than in the general population and trigger disease-disease interactions.

c) Concomitant medications: potential concerns associated with polypharmacy include increased pill burden, decreased medication adherence, and increased risk for pDDIs. This is a clinically relevant issue since heavy polypharmacy and pDDIs have been associated with adverse drug reactions, hospitalization, frailty, death, and reduced efficacy of both the antiretroviral and non-antiretroviral treatments [108].

d) Side effects: adverse events have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy, and for medication nonadherence [109–111]. More recent regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. However, active surveillance should be maintained. When symptoms are temporarily associated with exposure to an antiretroviral regimen and are not easily attributed to a known external cause, the possibility of switching to a safer option should be considered.

e) Medication adherence: due to longer half-lives and higher genetic barriers to resistance, modern ART medications are more forgiving of missed doses than before. This improvement has the potential benefit to allow more PWH achieve virological control with moderate adherence.

6.Long-term tolerability and safety of ART

6.1. Is ART toxicity still a real concern?

Perhaps in no field of pharmacology has substantial progress been made in such a short time as that achieved in the field of ART, making it increasingly tolerable and reducing its toxicity impact on

PWH. For instance, a young PWH, diagnosed at 18 years of age currently faces a 60-year expectation of ART, whose long-term toxicity is a complex problem, difficult to measure, and with a difficult-to-predict prognostic impact. Moreover, it may have an additive or synergistic effect on the aging process and the emergence of comorbidities. Many toxicities of the old drugs have almost completely disappeared, such as kidney and bone toxicities, while others, such as cardiovascular and metabolic toxicities, have been drastically reduced, although a possible cardiovascular risk signal has been reported in observational studies even in association with modern antiretrovirals [112–115]. The potential association of weight gain with integrase inhibitors and possibly related metabolic syndrome remains to be evaluated, taking into account the multifactorial nature of weight gain as well as the metabolic syndrome [78,116,117]. In addition, long-term exposure to any drug might have toxic potential, including NRTIs, which are widely used and currently included in all recommended first-line regimens [118–120]. Certainly, despite the drastic reduction in ART toxicity, a zero-risk drug does not exist and therefore the attention must always remain high in intercepting possible, even subclinical, toxicities [121]. This is even more important when new drugs or new formulations are introduced into clinical practice, as toxicities might not match those identified by clinical trials, due to their larger use in an unselected population with comorbidities, concomitant therapies and time of exposure to drugs that can be different from those explored in controlled studies. Assuming high treatment efficacy, the absence of toxicity remains a key determinant of long-term success and should be actively monitored along with other pharmacological and virological attributes of ART to ensure a good quality of life beyond virological success.

6.2. Adverse reactions and comorbidities

When evaluating the tolerability of ART, it is important to make a clear distinction between drug toxicity and comorbidities, as traditional risk factors appear more frequently and with earlier onset in PWH, probably as a function of the contribution of residual inflammation and of life styles [122,123]. An improvement in the characteristics of antiretrovirals has been inversely matched by a change in

the host. Therefore, it is clear that the major focus in terms of long-term safety must be placed on probing the vulnerability of each person, and on the intervention and management of modifiable risk factors, with special attention to polypharmacy, geriatric syndromes, and frailty, the presence of which directly correlates with the occurrence of adverse events [124]. A consequence of the progressive increase in comorbidities among PWH is the shift from the problem of drug-drug interactions to disease-disease interactions [125,126]. In other words, a minor or major therapeutic conflict can occur when treatment of one medical condition is relatively or absolutely contraindicated because of a co-existing condition. The possible criticalities of ART may be related not only to the risk of toxicity but also to the possibility of triggering or worsening comorbidities. For this reason, it is necessary to individualize ART by assessing the comorbidity profiles of PWH. In the context of a therapeutic alliance between physicians and patients, it is essential not to forget medical governance to distinguish between real or perceived tolerability problems. Proper medical governance remains the key to avoid the risk of compromising the virological efficacy of ART through inappropriate or untimely management [127–129].

6.3. The challenge of tolerability monitoring

Proper follow-up of tolerability is essential to guarantee long-term treatment success [130–132]. For this purpose, the physician's tasks should be:

a) correctly estimate the risk of comorbidities, trying to address modifiable risk factors;

b) evaluate subclinical damage to organs or systems prone to the most frequent comorbidities in PWH;

c) be able to set up first-level therapies for comorbidities and manage possible interactions with ART;

d) to implement and maintain robust professional referral relationships with a pool of dedicated specialists (cardiologists, nephrologists, endocrinologists, geriatricians, neurologists, psychiatrists) with specific expertise in HIV comorbidities;

e) staying up-to-date with the guidelines and applying them in monitoring PWH, even in view of the available resources, which can also be limited by critical issues such as the recent-SARS-CoV-2 pandemic;

f) building a therapeutic alliance with the person in treatment, in which choices are shared and confirmed by monitoring satisfaction and quality of life during ART.

7. People's satisfaction and quality of life

7.1. Fighting stigma and improving treatment adherence

The stigma perceived by PWH is a major obstacle in achieving optimal quality of life (QoL). It is multifactorial in nature and may, among many other factors, also be related to the daily assumption of ART [133]. In this regard, single-tablet regimens (STR) when compared to multi-tablet regimens, reduce privacy issues when taking tablets. Another obstacle to the achievement of an optimal QoL is, for some people, the stress of reminding them of HIV infection at the time of taking pills, disturbing their daily routine. Both STR and long-acting regimens can be favorable solutions to this condition, as well as useful strategies for improving adherence, as they reduce the number of times it is necessary to take therapy, and should be preferred when possible, according to patient preferences [134]. Combating stigma is also a key issue in improving adherence to ART. Indeed, PWH commonly report secrecy/stigma as a barrier to adherence, as well as depression, feeling sick, and alcohol/substance misuse, all factors related to suboptimal QoL, but also individual barriers such as forgetting, being away from home and a change to daily routine, and health service-related barriers, including distance to clinics and stock outs [135]. Medication supplies may also contribute to reduce the stigma as well

as promote adherence. The possibility of having a long-term supply corresponding to six monthly hospital visits or home delivery of medications avoid unnecessary hospital access [136]. Based on the same principle, a person-centered approach could allow for the same place and time of medical visits required for routine follow up, blood draws, and vaccinations, to reduce hospital access (Figure 2).

7.2. Quality of health integrated into services

A key aspect of HIV service delivery is to recognize the diverse needs of PWH towards a personalized medicine approach (Figure 2). The most frail or difficult-to-treat PWH might require additional interventions to be retained in care [137]. At the end of the spectrum, many healthy PWH might be bothered by "over-access" and ask to be treated at the primary care level. A personalized medical approach also requires information that directly questions the person in care, regarding lifestyle, symptoms and health-related quality of life through patient-reported outcomes (PROs) [132]. PROs assessment should be part of the routine evaluations promoting physician-patient interactions taking advantage of a telehealth approach. Community and HIV organization involvement may offer support in this holistic approach, reducing the digital divide affecting the most vulnerable individuals.

7.3. Innovation and personalized medicine

Personalized medicine describes a new clinical approach based on the individual characteristics of the person in care. Personalized medicine combines diagnostics and therapy with PROs and information regarding the patient's environment [138]. In this scenario, health-related QoL is the goal of the HIV cascade of care, the so-called "fourth 95," which ensures that, beyond HIV suppression, 95 percent of people with HIV have good quality of life [139]. PWH should be at the center of the model of care and be engaged in preventive, predictive, personalized, and participatory medicine (Figure 2). In this setting, healthcare workers not only take care of diseases but also become health coaches who coordinate personalized therapeutic and lifestyle interventions.

7.4. Integration with territorial and specialized health services

Another key aspect in achieving high-quality of services, and thus of health, is the interaction with general practitioners, who do not always have adequate expertise in the management of HIV medicine. The WHO global health sector strategy for HIV for the decade 2022-2030 includes an action calling for stronger integration of communicable and non-communicable disease services, suggesting that HIV should be put in the context of the management of chronic disease conditions [140]. On the one hand, access to the infectious disease outpatient clinic should be facilitated with free and direct access options in all centers, at least in a guaranteed daily time slot. On the other hand, it would be appropriate to organize HIV medical educational activities involving general practitioners, non-infectious disease specialists taking care of HIV comorbidities, and physicians working in residences for older PWH (Figure 2). In addition, dedicated funding is needed for the implementation of new HIV management pathways outside hospitals to meet the diverse needs of PWH, organize education, new antiretroviral drug delivery systems, computer systems for remote communication between healthcare workers and patients, and support resources for social and psychological aids.

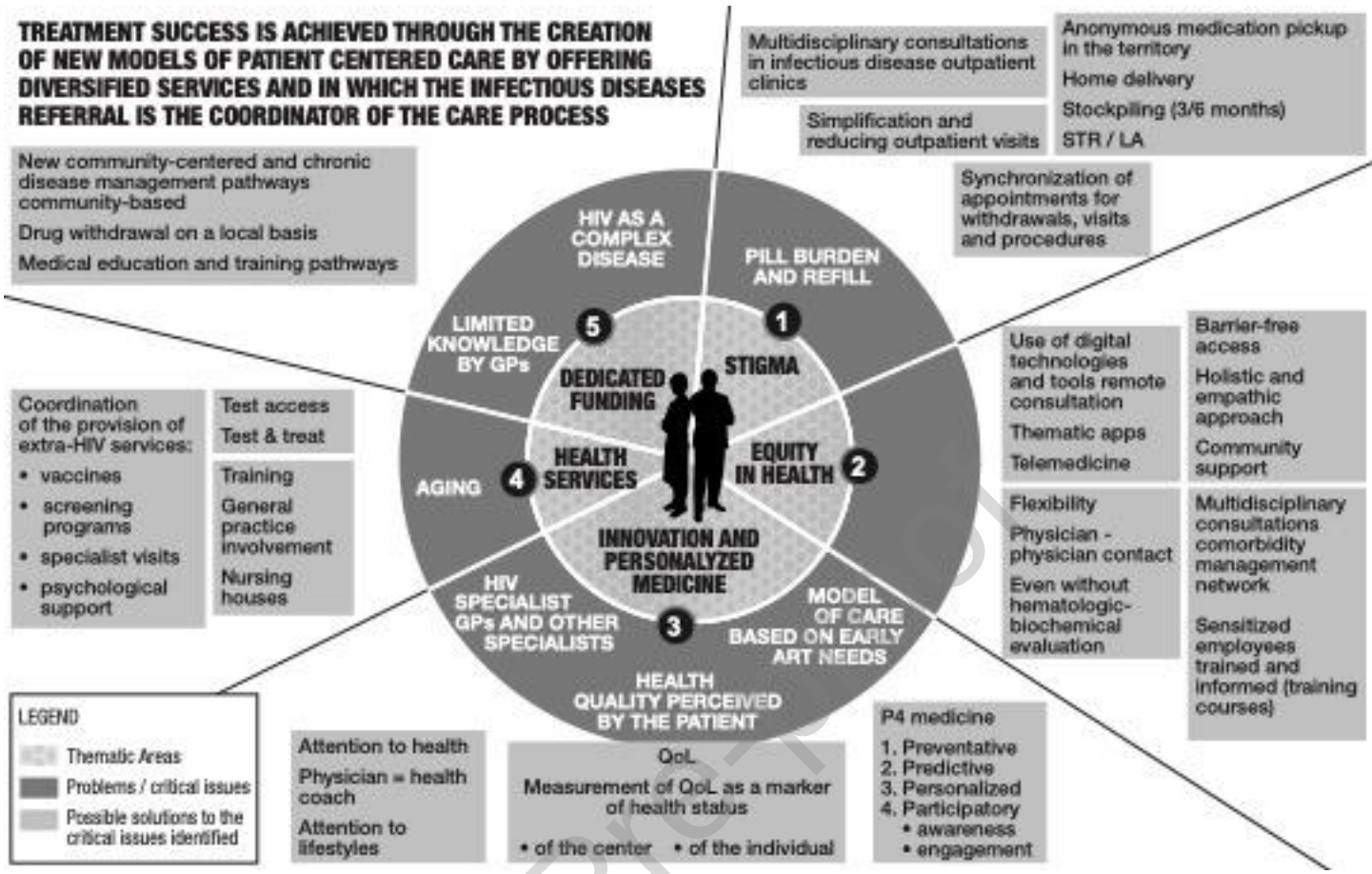


Figure 2. Unmet needs and possible solutions for building a patient-centered approach to HIV care.

8.Conclusions

In conclusion, several key points should be considered:

- The attributes that current ART must ensure to meet the ambitious goal of long-term treatment success are a high genetic barrier to resistance; long-term efficacy; optimal long-term safety and tolerability profile; simplicity and ability to ensure good quality of life.

- The goals of HIV treatment and ART selection are to durably suppress viral replication, maintain good health, improve the well-being of PWH, and prevent HIV transmission. Successful ART for PWH improves Quality of Life.

- Rapid achievement of viral suppression is an important goal for an ART regimen. PWH do not transmit HIV when their viral load is undetectable ("undetectable = untransmittable" or "U = U"), resulting in both individual and public health benefits.

- Nonadherence to ART can be difficult to predict in real-world settings and is associated with treatment failure and sometimes drug resistance. To maximize adherence ART regimens should be simple, convenient, well tolerated, and eventually forgiving of suboptimal adherence.

- As PWH live longer, they can develop non–AIDS-related comorbidities, including cardiovascular, bone, and chronic kidney diseases, which affect Quality of Life and are costly to treat. An ART regimen should be selected that does not cause or exacerbate these comorbidities or complicate their treatment. Attention to the maintenance of a healthy lifestyle is an important part of HIV management for all PWH.

In the modern ART era, long-term treatment success should be intended as a combination of HIV-RNA suppression, possibly below the threshold of TND (as a result of a potent, high-genetic barrier and high-forgiveness regimen) and a person-centered approach, based on the individual therapeutic history, GRT, past toxicities and comorbidities. This should be based on the perceived tolerability and quality of life, considering the preferences of people on treatment along with the virological and

pharmacological factors. The health care system should facilitate universal and rapid access to personalized, robust, and effective therapies. The ultimate goal of this patient-centered model of care should consider both physical and psychological health in achieving a high Quality of Life and long-term treatment success.

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Declaration of Competing Interest

This study was supported by an unrestricted grant from Gilead. The company had no role in designing the study, collecting or analyzing the data, interpreting the results, or writing or approving the article.

Outside the submitted work, LT attended advisory boards or served as consultant or received grants for conferences participations from Gilead Sciences, ViiV Healthcare and Janssen and research grants for her institution from Gilead Sciences; ADB has received speakers' honoraria from Gilead, ViiV, Janssen-Cilag, has been advisor for ViiV, Janssen-Cilag, MSD and had received grant for research from Gilead. MS has received funds for attending symposia, speaking and organizing educational activities from ViiV Healthcare, Janssen-Cilag and Theratechnologies. EF received speakers' honoraria, research grants and advisory board fees from Viiv Healthcare, Gilead Sciences, Merck Sharp & Dohme and SOBI.

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CRediT authorship contribution statement

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