

## Redefining therapeutic success in HIV patients: an expert view

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Thanks to advances in the field over the years, HIV/AIDS has now become a manageable chronic condition. Nevertheless, a new set of HIV-associated complications has emerged, related in part to the accelerated ageing observed in people living with HIV/AIDS, the cumulative toxicities from exposure to antiretroviral drugs over decades and emerging comorbidities. As a result, HIV/AIDS can still have a negative impact on patients' quality of life (QoL). In this scenario, it is reasonable to believe that the concept of therapeutic success, traditionally associated with CD4 cell count restoration and HIV RNA plasma viral load suppression and the absence of drug resistances, needs to be redefined to include other factors that reach beyond anti-retroviral efficacy. With this in mind, a group of experts initiated and coordinated the RET Project, and this group, using the available evidence and their clinical experience in the field, has proposed new criteria to re-define treatment success in HIV, arranged into five main concepts: rapid initiation, efficacy, simplicity, safety, and QoL. An extensive review of the literature was performed for each category, and results were discussed by a total of 32 clinicians with experience in HIV/AIDS (4 coordinators + 28 additional experts). This article summarizes the conclusions of these experts and presents the most updated overview on the five topics, along with a discussion of the experts' main concerns, conclusions and/or recommendations on the most controversial issues.

### Introduction

The introduction of HAART has improved health, prolonged life and substantially reduced the risk of HIV transmission,<sup>1</sup> to the extent that HIV/AIDS has now become a treatable chronic disease. Despite these positive aspects, a set of HIV-associated complications persist, related in part to the accelerated or premature ageing observed in some people living with HIV (PLWH), cumulative toxicities resulting from exposure to antiretroviral drugs over decades, and other comorbidities.<sup>1,2</sup> Furthermore, despite ART efficacy, treatment does not seem to fully restore increased inflammation and immune health<sup>1,3</sup> and the appearance of complications such as cardiovascular disease and cancer has not decreased accordingly.<sup>1</sup> We also now know that some chronic diseases, including stroke, lung diseases, diabetes, cardiovascular diseases, hypertension, cancers and neurocognitive disorders, can occur more often in PLWH than in people without HIV,<sup>4–8</sup> and that many of these factors may interact, so it is essential that chronic comorbidities are controlled in these patients.<sup>2</sup> As a result, the quality of life (QoL) of PLWH may still be generally lower than in the general population,<sup>9</sup> and ART characteristics (i.e. efficacy, side effects, pill

burden) and their impact on patients' preferences emerge as the main focus of several studies.<sup>10</sup> Finally, multiple comorbidities have become an important concern for some healthcare systems, particularly those in resource-limited regions that have yet to fully develop a chronic care model.<sup>1</sup>

Traditionally, the concept of therapeutic success has been associated with CD4 cell count restoration, plasma RNA-HIV suppression, and the absence of emerging HIV drug resistance mutations and severe toxicity. As mentioned above, the fact that HIV/AIDS has become a manageable chronic condition has highlighted the need to consider other factors when assessing ART success. For this reason, a group of experts initiated and coordinated the RET (the acronym for *Redefinition of Therapeutic Success* in Spanish) Project, the main aim of which was to redefine therapeutic success in PLWH. Based on the available evidence and on the experts' clinical experience in the field, the group agreed that overall ART therapeutic success in PLWH should be defined according to five main concepts: efficacy, safety, rapid initiation, simplicity and QoL, each of which should include different areas for ART improvement. Accordingly, an extensive review of the literature was performed.

This work aimed to identify not only the areas in which agreement and general consensus existed, but also those gaps not covered by the current evidence and that, as such, would need to be further explored and given special consideration. The final conclusions were discussed and aligned by 32 collaborating Spanish clinicians with broad experience in HIV/AIDS (4 main coordinators + 28 additional experts).

This article summarizes the conclusions of the panel on the main topics that redefine the concept of therapeutic success (Table 1 and Figure 1). Each topic is discussed in a specific section as follows: efficacy of ART; simplicity of ART; rapid initiation of ART; safety, toxicity and interactions; and QoL. Each of the five sections was then divided into different subsections that cover the most recent evidence in the field (current status), and the experts' main concerns, conclusions and/or recommendations regarding the most controversial issues (areas for improvement).

## Rapid initiation of ART

### Current status

Delayed initiation of ART may be associated with negative health effects for PLWH and with an increased risk of transmission.<sup>11</sup> Therefore, in all patients, ART should be initiated as soon as possible. Indeed, immediate (same-day HIV diagnosis) or rapid initiation of ART (initiation regardless of knowing the results of baseline tests) have been proposed to improve treatment outcomes.<sup>12</sup> However, it is worth mentioning that the available evidence comes from studies conducted mainly in low-income countries. This is the case of the unblinded, randomized trial of standard ART initiation versus same-day HIV testing and ART initiation conducted in patients from Haiti with CD4 count  $\leq 500$  cells/mm<sup>3</sup> and no clinical complications ( $N = 762$ ).<sup>12</sup> At 12 months, rapid ART initiation was associated with a higher retention in care with HIV-1 RNA  $< 50$  copies/mL [53% versus 44%; relative risk (RR) 1.21, 95% CI 1.04–1.31,  $P = 0.012$ ]. In this setting, same-day HIV testing and ART initiation were seen to be feasible and beneficial, improving retention in care and virological suppression among patients with early clinical HIV disease. These results were supported by a systematic review, in which the analysis of 22 studies revealed that accelerated ART initiation ( $< 14$  days) could lead to improved clinical outcomes.<sup>13</sup> In another systematic review evaluating the impact of rapid ART initiation (7 days after HIV diagnosis) on virological control and mortality in seven studies ( $N = 18011$ ) conducted in low- and middle-income countries,<sup>11</sup> greater virological control (RR 1.18, 95% CI 1.11–1.35) and a lower mortality rate (RR 0.72, 95% CI 0.51–1.01) were reported, although differences were not statistically significant. Improved retention in care and better adherence were also observed 12 months after rapid ART initiation. The authors concluded that the studies demonstrated positive effects for rapidly delivered ART when combined with several setting-specific cointerventions (i.e. home follow-up, social assistance, patient's accessibility to the hospital, etc.).<sup>11</sup>

Among the studies conducted in high-income countries, two were carried out in the United States and another included patients from various Western countries. The first, conducted in patients from a large HIV clinic in Atlanta, assessed the feasibility and effectiveness of a rapid entry programme [the Rapid Entry and

ART in Clinic for HIV (REACH) program] on improving time to ART initiation and time to viral suppression.<sup>14</sup> In a population with unique characteristics (90% black, 57% uninsured, 44% drug users), time to virological suppression fell from 77 days in the pre-REACH era to 57 days in the post-REACH era ( $P < 0.002$ ). Time to first attended provider visit and time to ART initiation also fell from 17 to 5 days and from 21 to 7 days, respectively ( $P < 0.0001$  in both cases). These results suggested that rapid entry is feasible and could have a positive impact on HIV transmission at the population level. The second study was a retrospective review to describe virological outcomes from the San Francisco-based Ward 86 Rapid ART Program for Individuals with an HIV Diagnosis (RAPID) ART program.<sup>15</sup> In the study population, evaluated between 2013 and 2017 ( $N = 225$ ; 51.4% with substance use, 48.1% with mental health diagnoses, 30.6% unstably housed), 95.8% achieved viral suppression to less than 50 copies/mL by 1 year after intake. Furthermore, plasma viral load (PVL) remained undetectable in 92% of patients at the last recorded visit (median follow-up 1.09 years, 0–3.92). This study demonstrated that the rapid initiation of ART for vulnerable populations is feasible and effective, although it requires significant multidisciplinary care and municipal support. The third study, the DIAMOND trial,<sup>16</sup> was a prospective study evaluating the efficacy and safety of a single-tablet regimen (STR) (darunavir/cobicistat/emtricitabine/tenofovir alafenamide) in a rapid initiation model of care in several Western countries. Results showed a high therapeutic success rate at 48 weeks (84%), with no virological failures, as well as high treatment satisfaction among participants. Recently, new data on test and treat with darunavir/lamivudine have been published. In the STAT trial,<sup>17</sup> a rate of viral suppression of 87% at 24 weeks was reported in the study population, and 74% as per the FDA snapshot algorithm.

Finally, the WHO has issued important guidelines regarding ART initiation,<sup>18</sup> strongly recommending that rapid ART initiation (within 7 days) should be offered to PLWH following confirmed diagnosis and clinical assessment (high-quality evidence for adults and adolescents; low-quality evidence for children). The WHO furthermore strongly recommends ART initiation on the same day as HIV diagnosis based on the individual's willingness and readiness to start ART immediately (high-quality evidence for adults and adolescents; low-quality evidence for children). Rapid initiation is also recommended by all clinical guidelines.<sup>19–22</sup> Importantly, it is not necessary to wait until baseline test results are available (including HLA-B\*5701, HBV, PVL, CD4 cell count and genotypic resistance study results) before starting treatment, as long as the use of the regimen of choice does not depend on these results.<sup>21,22</sup> However, not all studies have shown similar results in this regard. For example, the STAT study,<sup>17</sup> including HIV patients with resistance mutations at baseline or HBV co-infection requiring modifications of their ART regimens, suggested that efficacy changed depending on PVL and CD4 cell count. Furthermore, various studies have been performed<sup>16,17,23</sup> to evaluate the feasibility of different treatments in a rapid test and treat model of care (some of which, such as the RoChHa study,<sup>23</sup> are currently ongoing), in order to assess the regimens recommended as a preference or alternative by most clinical guidelines. Outcomes have been diversely successful and could be taken into consideration when establishing a test and treat strategy.

**Table 1.** Summary of areas for improvement/recommendations in the five main areas that define ART therapeutic success in PLWH

Rapid initiation	Efficacy	Simplicity	Safety	Quality of Life
Start ART on the same day of HIV diagnosis or on the first attended provider visit	Define response to ART or treatment failure by a PVL threshold of <50 copies/mL	Consider ART simplicity when assessing therapeutic success	Evaluate baseline BMD in postmenopausal women, subjects with bone disease, or with factors associated with an increased risk of osteoporosis, FRAX score >10%, as well as with age $\geq$ 50 years, and in all individuals treated with TDF	Emphasize comprehensive healthcare to ensure that patients have a better QoL
Incorporate ART initiation into the standard of care	Prioritize initial ART regimens that have demonstrated high rates of optimal viral suppression in clinical trials	Administer simple regimens (STRs) as an essential element in the care of PLWH	Avoid the use of TDF especially in subjects with or at risk of osteopenia or osteoporosis. Also avoid TDF in subjects with any kind of renal disease or higher susceptibility of developing it	Implement strategies addressed specifically at improving QoL in HIV care programmes. ART should contribute to this by being simpler, better tolerated and less toxic
Prioritize regimens not requiring prior availability of test results, including triple-drug regimens based on DTG, BIC or DRV/c	Prioritize regimens with low virological failure rates regardless of baseline PVL		Use TAF over TDF in boosted regimens that must include tenofovir	Assess HRQoL in PLWH; use PROs when possible
	Include outcomes from subjects with high baseline PVL in clinical evaluations		Systematic renal toxicity monitoring is not required when using TAF, ABC or dual regimens with DTG (DTG/3TC or DTG/RPV)	Preferentially use tools for measuring QoL in PLWH that can be performed in a reasonable time, that explore at least the physical, social and mental/emotional domains and that have been validated in people with HIV, and, preferentially, in every geographic context and language
	Prioritize the use of initial ART regimens that have demonstrated low rates of virological failure regardless of a CD4 count <200 cells/mm <sup>3</sup>		Regular blood pressure monitoring at 6 monthly visits, along with treatment for other cardiovascular-related pathologies if required	Use WHOQOL-HIV-BREF validated questionnaire in Spain
	Prioritize ART regimens that achieve a faster undetectable HIV PVL (especially in situations of high risk of transmission)		If possible, change ART regimen in subjects with a $\geq$ 10% 10 year risk of CVD to an appropriate regimen, including NNRTIs (RPV or DOR), or non-boosted INSTIs	Developing actions to correct low-scoring HRQoL factors detected when applying these tools should be a priority
	Prioritize ART regimens associated with low probability of developing 'blips'		Avoid ABC in subjects with moderate or high cardiovascular risk	Include PRO questionnaires in double-blind randomized clinical trials of new ARTs

Continued

**Table 1.** *Continued*

Rapid initiation	Efficacy	Simplicity	Safety	Quality of Life
	Prioritize the use of ART regimens that are less likely to develop resistance mutations in virological failure		Monitor body weight and BMI at every 6 month visit. Consider ART change if significantly greater weight gain than expected is detected not justified by other causes	Use available electronic tools (devices, websites, applications) to facilitate PRO research and contribute to improving the QoL of patients. These tools should be adapted to each population, well integrated into clinical management and easily accessible and understandable.
			Actively assess NAFLD in PLWH, especially in the presence of obesity, diabetes mellitus and lipodystrophy. Administer metabolic neutral ART schemes to these patients	Include measures to assess stigma and to evaluate its impact on the patient's QoL
			Actively assess possible ART-related neuropsychiatric events and consider the possibility of a change of regimen	Inform people with HIV on ART that once they reach undetectable PVL and maintain it for more than 6 months, and if treatment adherence is appropriate, virus transmission through sex is highly unlikely
			If possible, choose regimens with a lower DDI potential. If chemsex is practised, indicate regimens with a long half-life and a long forgiveness period. Avoid boosted regimens including cobicistat or ritonavir	

3TC, lamivudine; ABC, abacavir; BIC, bictegravir; BMD, bone mineral density; CVD, cardiovascular disease; DDI, drug–drug interaction; DRV/c, darunavir/cobicistat; DTG, dolutegravir; DOR, doravirine; FRAX, fracture risk assessment tool; HRQoL, health-related quality of life; INSTIs, integrase strand transfer inhibitors; NAFLD, non-alcoholic fatty liver disease; PLWH, people living with HIV; PROs, patient-reported outcomes; PVL, plasma viral load; QoL, quality of life; RPV, rilpivirine; STR, single-tablet regimen; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; WHOQOL-HIV-BREF, WHO Quality of Life in HIV-infected Persons instrument.

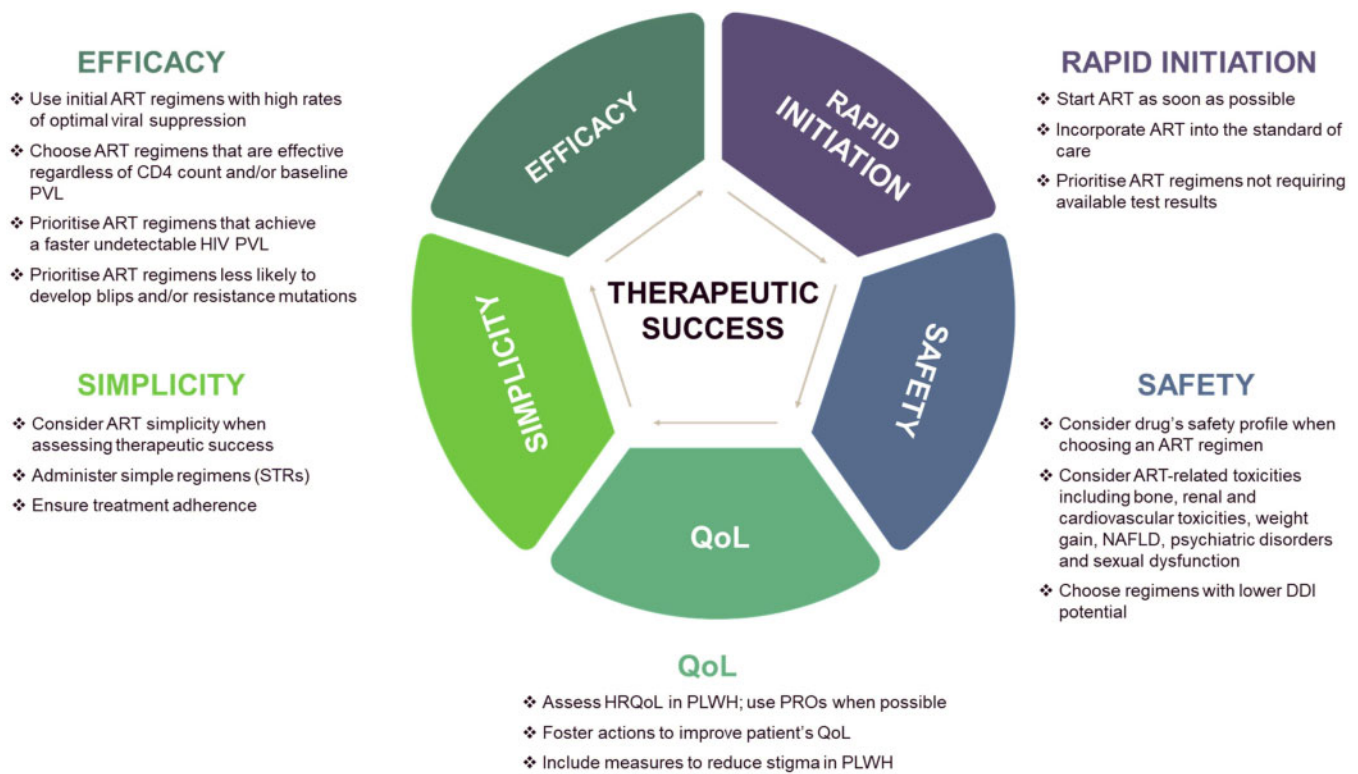
### Areas for improvement

In conclusion, rapid ART initiation has been associated with greater retention in care, better virological control and better overall outcomes than standard initiation in low–middle income countries. However, evidence of the benefits of rapid ART initiation in Western countries is not yet sufficient. Therefore, producing more evidence in settings where the information is still lacking would be an important aspect to further support this recommendation. Another important consideration is that individuals who rapidly initiate ART appear to be satisfied with the strategy.

Consequently, in line with the WHO recommendations and the available evidence, we suggest that if the patient is willing, starting ART on the same day of HIV diagnosis or on the first attended

provider visit may be beneficial. Therapeutic regimens that allow immediate/rapid ART initiation without the results of the initial analytical evaluation are currently available. Finally, we strongly believe that rapid ART initiation should be incorporated into the standard of care in order to optimize results. Efforts must be made by health administrations to ensure that rapid ART initiation can be implemented in any HIV unit.

If rapid ART initiation is selected, it is important to prioritize regimens with a high barrier against resistance development, low toxicity, anti-HBV activity and a low rate of drug–drug interactions (DDIs). These regimens can begin without waiting for test results that may delay treatment initiation, and include triple-drug regimens with tenofovir (tenofovir alafenamide or



**Figure 1.** Cycle diagram showing the five concepts proposed for the redefinition of therapeutic success in HIV patients and the key recommendations/areas for improvement for each of them. DDI, drug–drug interactions; HRQoL, health-related quality of life; NAFLD, non-alcoholic fatty liver disease; PLWH, people living with HIV; PROs, patient-reported outcomes; PVL, plasma viral load; QoL, quality of life; STRs, single-tablet regimens. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

tenofovir disoproxil fumarate) based on dolutegravir, bictegravir or darunavir/cobicistat.

## Efficacy of the ART

### Suppression of PVL

#### Current status

Since the early years of the HAART era, PVL suppression has been demonstrated to be an excellent marker for non-progression to AIDS.<sup>24,25</sup> Thus, as reported in more than 1300 infected patients enrolled in seven different clinical trials, the risk of a new AIDS-defining event or death after 24 weeks of treatment is reduced in proportion to the magnitude of the reduction of HIV-1 RNA levels (adjusted for baseline levels).<sup>24</sup> Based on the evidence, current clinical guidelines identify attaining maximal and durable PVL suppression as the main objective and best marker for response to ART,<sup>19–22,26</sup> although the definition of virological failure differs among the different recommendations. Thus, the majority of guidelines define HIV RNA levels <50 copies/mL as a correct virological suppression,<sup>20,21</sup> and virological failure is defined as a confirmed level of >200 copies/mL.<sup>26</sup> On the other hand, values between 50 and 200 copies/mL are more difficult to interpret, and an association has been observed between persistently detectable viraemia (HIV RNA <50–200 copies/mL) and virological failure.<sup>27</sup> Currently, several commercial assays are capable of detecting PVL <50 copies/mL

(up to 20 copies/mL). A threshold below that level has not demonstrated additional clinical benefits.<sup>20–22</sup>

'Blips' are defined as transient, isolated, low-level increases of 50–200 copies/mL in HIV viral load preceded and followed by a PVL <50 copies/mL with no ART regimen change that, when occurring in isolation, lack clinical impact.<sup>21</sup> However, frequent blips have been associated with an increased risk of virological failure and emergence of drug resistance mutations, particularly when using regimens with a low barrier against the development of resistance mutations.<sup>28,29</sup>

#### Areas for improvement

Based on the evidence, it is therefore reasonable to believe that response to ART or treatment failure must be defined by a PVL threshold of <50 copies/mL. Furthermore, we do not consider the use of a higher threshold (200 copies/mL) appropriate, despite the recommendation issued by some guidelines,<sup>22</sup> while we have evidence that a persistent PVL of 50–200 copies/mL is associated with a higher risk of virological failure. Likewise, we do not consider the use of lower thresholds (<40 copies/mL) necessary because no evidence is available on their potential advantages and/or disadvantages. Priority should be given to the use of initial ART regimens that have demonstrated high rates of optimal viral suppression in clinical trials. However, until more data are available, patients with viral loads that are detectable but below 50 copies/mL should be considered as individuals with suppressed viral load.

On the other hand, the use of initial ART regimens associated with a low probability of developing ‘blips’ should be prioritized. It is advisable to monitor blip frequency in clinical trials, given the putative differences between the new therapeutic regimens available. It is crucial to assess the frequency (if any) of the peaks and their further risk with virological failure in those integrase strand transfer inhibitor (INSTI)-based regimens.

### **Patients with HIV RNA above 100 000 copies/mL**

#### *Current status*

The efficacy of ART also depends on baseline PVL. Some results suggest that in ART-naive individuals, PVL may increase over time and more sharply in older individuals, and that a higher viral load is strongly associated with an ongoing rate of CD4 cell count depletion.<sup>30</sup> Furthermore, full HIV RNA suppression may take longer in patients with HIV-1 RNA  $\geq 100\ 000$  copies/mL, and this delay might subsequently increase the chance of treatment-emergent resistance to certain antiretrovirals.<sup>31</sup> Indeed, some regimens were less effective when initiated in patients with high PVL. For example, in two randomized double-blinded clinical trials (THRIVE<sup>32</sup> and ECHO<sup>33</sup>), the incidence of failure and the emergence of drug resistance mutations among patients with baseline HIV RNA  $>100\ 000$  copies/mL was higher in those receiving rilpivirine + tenofovir disoproxil fumarate/emtricitabine than in the comparator group treated with efavirenz + tenofovir disoproxil fumarate/emtricitabine. We focus on regimens that are currently the preferred used.

#### *Areas for improvement*

To be considered optimal, an initial ART must have demonstrated low virological failure rates regardless of baseline PVL (in patients with either  $<$  or  $\geq 100\ 000$  copies/mL), and priority should be given to those treatments. Additionally, for a correct assessment of the efficacy rate of new ART strategies, outcomes from subjects with high baseline PVL need to be included in clinical evaluations.

### **Patients with late diagnosis of HIV infection**

#### *Current status*

CD4 cell count is another important factor determining the efficacy of the ART. Some regimens are less effective in patients with low CD4 cell count at baseline, including dolutegravir + lamivudine and rilpivirine/tenofovir disoproxil fumarate/emtricitabine.<sup>34</sup> In the subgroup analysis of the GEMINI studies, patients who started dolutegravir + lamivudine with a baseline CD4 count  $<200$  cells/mm<sup>3</sup> showed a lower efficacy rate than patients treated with dolutegravir/lamivudine/tenofovir disoproxil fumarate in snapshot analyses at 48, 96 and 144 weeks.<sup>35</sup> However, those differences were not only associated with a higher proportion of virological failure. Seemingly the ECHO<sup>33</sup> and THRIVE<sup>32</sup> trials demonstrated higher virological failure rates when patients with a baseline CD4 count  $<200$  cells/mm<sup>3</sup> were treated with rilpivirine. Finally, many patients with late diagnosis of HIV may present AIDS conditions (infection opportunistic and/or tumours) at the time of diagnosis.<sup>36</sup> In this scenario, DDI between antiretroviral drugs and those drugs necessary for the treatment of opportunistic events are common and can lead to a greater or lesser exposure to drugs that can

increase the frequency and/or severity of toxicities or affect the therapeutic response. This fact should be considered when choosing the antiretroviral treatment regimen.

#### *Areas for improvement*

Overall, these data underline the advisability of giving priority to initial ART regimens that have demonstrated low rates of virological failure regardless of CD4 count  $<200$  cells/mm<sup>3</sup>. If safe alternatives are available, strategies with doubtful efficacy in this scenario or those that lack supporting evidence should be avoided. In patients with late diagnosis of HIV infection and concomitant opportunistic events, it is necessary to use a regimen with a lower DDI potential, adjusted to the drugs necessary for the treatment of opportunistic events and specifically not including pharmacokinetic enhancers.

### **Prevention of HIV transmission**

#### *Current status*

In PLWH, ART reduces HIV transmission and the spread of the virus in a population.<sup>37</sup> In the HPTN 052 trial,<sup>38</sup> the initiation of ART in the HIV-infected partners of serodiscordant couples resulted in a 96% reduction in the risk of transmission. Transmission was observed in only eight couples receiving ART; four transmissions occurred before the index patient achieved virological suppression and another four occurred during index patient virological failure.<sup>39</sup> No transmission was observed in partners of patients with stable HIV RNA  $<50$  copies/ $\mu$ L.<sup>39</sup> Similar results were observed in the Opposites Attract cohort study that analysed couples from Australia, Brazil and Thailand,<sup>40</sup> and in the PARTNER 1 and 2 cohort trials,<sup>41,42</sup> carried out in 1110 serodiscordant homo- and heterosexual couples. In the case of vertical transmission of HIV, it is worth considering that this is an exceptional event in pregnant women who have suppressed PVL.<sup>43</sup> In line with these findings, the ‘Undetectable=Untransmittable’ (U=U) campaign has emerged, proposing that the sooner undetectability is achieved, the earlier HIV transmission will be stopped.<sup>41</sup> This strategy has had a huge positive impact on the stigma of PLWH. Regarding the time to virological suppression (TVS), several regimens have been evaluated. Among those carried out with INSTIs versus other ART regimens, we should mention the SINGLE study,<sup>44</sup> in which the TVS was shorter with dolutegravir + abacavir/lamivudine compared with efavirenz/emtricitabine/tenofovir disoproxil fumarate (28 versus 84 days,  $P < 0.0001$ ), the FLAMINGO study,<sup>45</sup> which showed a shorter TVS with dolutegravir than with ritonavir-boosted darunavir, and the STARTMRK<sup>46</sup> and ACTG 5257<sup>47</sup> studies, with shorter TVS for raltegravir compared with efavirenz and ritonavir-boosted atazanavir or to ritonavir-boosted darunavir, respectively. High efficacy in terms of TVS has been shown in studies with integrase inhibitors (INIs), as in the 1489,<sup>48</sup> 1490,<sup>49</sup> SPRING-2<sup>50</sup> and GEMINI<sup>35,51</sup> studies.

#### *Areas for improvement*

Priority should be given to using antiretroviral regimens that achieve a faster undetectable HIV PVL. This recommendation is especially relevant in situations involving high risk of onward

HIV transmission in the patient's environment and in pregnant women.

Guidelines from most regions recommend INSTI-based regimens as first-line ART. The use of INSTI-based regimens has the advantage of being faster to reach an undetectable viral load, and this may have an impact on reducing HIV transmission. However, in some regions these recommendations have not been adequately implemented. In this scenario, it is important that health policy encourages HIV programmes to properly implement these guidelines.

## Development of drug resistance mutations

### Current status

The question whether virological 'blips' predict adverse clinical outcomes, such as virological failure or rebound, has been a controversial issue in the literature for many years.<sup>28</sup>

The barrier against resistance development impacts the development of drug resistance mutations in the virological failure. It is known that this phenomenon is not homogeneous among the different starting ART regimens.<sup>21</sup> Thus, no resistance mutations with bicitgravir/tenofovir alafenamide/emtricitabine, dolutegravir/abacavir/lamivudine and dolutegravir/tenofovir alafenamide/emtricitabine regimens were reported in the follow-up of their pivotal clinical studies.<sup>48–50,52</sup> Although the development of resistance with the rest of the preferential or alternative regimens with a lower genetic barrier is rare, it may affect two families of ART.<sup>21</sup> Recently, a second case of virological rebound with two-class resistance selection with dolutegravir + lamivudine was reported, associated with low treatment adherence, and selection of resistance mutations against both dolutegravir and lamivudine (namely, M184V and R263K mutations).<sup>53</sup> While this event is still uncommon, attention must be paid to subjects with irregular adherence to this regimen.

### Areas for improvement

Given the impact of drug resistance mutations on treatment efficacy and the limitations of subsequent ART options, it seems reasonable to give priority to the use of ART regimens that are less likely to select resistance mutations in virological failure.

## Simplicity of the ART

### Current status

It is considered that adherence is equally as important as the potency of a regimen, while the complexity of medication regimens is a known determinant of adherence across a range of chronic diseases.<sup>54</sup> In line with this, the administration of simple co-formulated regimens has been associated with better adherence and therapeutic success in HIV patients.<sup>55,56</sup> Indeed, from the early days of ART combinations, patients reported their preferences for simpler regimens that can be achieved by reducing the number of pills or the dosing frequency.<sup>54,55,57</sup>

Among the factors influencing adherence to ART in naive patients, an observational study conducted between 2011 and 2016 in 27 216 patients from the USA identified ethnicity, income level and the use of STRs.<sup>58</sup> Thus, only 43% of patients presented adequate adherence, with lower rates among blacks and

Hispanics, and participants with lower incomes. Importantly, the use of STRs was associated with better adherence than multi-tablet regimens (MTRs) in patients on INSTI-based regimens (49% versus 24%, RR 2.16), but no significant difference was observed among those on NNRTI-based regimens (45% versus 45%, RR 1.12). Several studies have analysed the specific advantages of reducing the number of pills in HIV patients. Thus, in a systematic review and meta-analysis evaluating the relationship between STRs versus MTRs, treatment adherence and viral suppression,<sup>59</sup> the authors found that STRs were associated with higher treatment adherence than MTRs in 10 out of 11 observational studies, with a 63% greater likelihood of achieving  $\geq 95\%$  adherence. Additionally, higher adherence rates were associated with higher levels of viral suppression in 13 out of 18 studies. In another meta-analysis aimed at comparing 48 week treatment outcomes (adherence, efficacy, safety/tolerability and costs) with STRs versus MTRs,<sup>60</sup> patients on STRs were significantly more adherent (OR 1.96,  $P < 0.001$ ), more likely to achieve virological suppression (RR 1.05,  $P = 0.002$ ), reported higher therapy satisfaction, better symptom control and improved health status than those on MTRs, although no differences were found regarding CD4 count or safety. Furthermore, STRs also reduced healthcare resource utilization and demonstrated cost-effectiveness compared with MTRs, and a trend toward lower discontinuation rates with the former was observed. Importantly, the benefits of STRs were demonstrated regardless of the number of doses per day.

Reducing the number of doses, another effective way of simplifying treatments for HIV patients, was explored in a meta-analysis of 11 randomized controlled trials ( $N = 3029$ ). This study included both naive and pre-treated patients and analysed the impact of once-daily (q24h) versus twice-daily regimens on treatment adherence.<sup>61</sup> The results revealed that the adherence rate was better with q24h regimens (+2.9%; 95% CI 1.0%–4.8%,  $P < 0.003$ ) than with twice-daily regimens, with no differences in overall virological efficacy. The observed effect was more pronounced at the time of treatment initiation and for regimens in which all medications were taken once a day. Finally, a higher virological suppression rate was observed with the initial treatment (+5.7%; 95% CI 0.7%–10.8%,  $P < 0.001$ ). Other studies have evaluated the impact of reducing dose frequency in long-term regimens (every 4–8 weeks). In clinical trials investigating changing treatment in patients with suppressed PVL, the administration of intramuscular drugs every 4 weeks had a similar efficacy to that of the daily oral maintenance treatment.<sup>62–64</sup> Besides, in these trials, the proportion of patients who were adherent and remained in treatment was also similar in patients with daily or 4 weekly treatments;<sup>62–64</sup> the 4 weekly intramuscular administration being the one that showed higher levels of treatment satisfaction according to patient preference.<sup>63</sup> In a later study, administration every 8 weeks was shown to be non-inferior to 4 weekly dosing.<sup>65</sup>

### Areas for improvement

Based on the available data, PLWH prefer simple regimens, with as few doses and pills as possible. Furthermore, ART regimens with a low number of pills and low dosing frequency are associated with better adherence, and some strategies to simplify ART are associated with better virological control. STRs prevent selective non-compliance and thus reduce the risk of resistance selection

due to partial non-adherence. We believe that the simplicity of ART must be a factor to be considered when redefining therapeutic success because data from clinical trials and observational studies favour the use of STRs administered on a once-daily basis to improve treatment adherence and virological response. Furthermore, in some patient profiles, especially those with low adherence rates, we believe that simpler and easier ways of administration, such as those provided by STRs, would be beneficial. Consequently, the administration of simple regimens should be considered an essential element in the care of people with HIV.

## Safety: toxicity and interactions

### Importance of toxicity in the redefinition of therapeutic success

#### Current status

In Phase III registrational randomized clinical trials, discontinuation rates due to ART-related adverse events (AEs) have been greatly reduced (<1%–2% at 48 weeks, and occasionally even to 0%) thanks to the safety of current ART listed as preferred or recommended in the main clinical guidelines.<sup>20,21,33,35,38,45–50,52,66–72</sup> Among the drugs tested in those trials, raltegravir, bicittegravir, dolutegravir, elvitegravir/cobicistat, rilpivirine and darunavir/cobicistat in combination with tenofovir alafenamide, abacavir, tenofovir disoproxil fumarate or only lamivudine are included. They present a favourable safety profile compared with other alternatives and, consequently, should be used preferentially. Furthermore, their drug-related toxicity rates (any grade or G3/4) are significantly reduced.<sup>20,21,33,35,38,45–50,52,66–72</sup>

Several low-grade AEs have been described as frequent (>5%) in clinical trials, and these, despite not usually leading to treatment discontinuation in those trials, may limit patients' QoL and eventually cause discontinuation in real life. These AEs include headache, fatigue, insomnia, anxiety, abnormal dreams and nausea, and may occur with most of the drugs.<sup>73–77</sup> If they are not properly addressed by questioning patients in a targeted manner, they can go unnoticed or be attributed to other causes.

#### Areas for improvement

Regimens currently considered as preferential for treatment initiation or simplification are associated with low toxicity rates and low toxicity-related discontinuation rates, favouring compliance and contributing to better patient QoL. Consequently, it is important to take the drug's safety profile into consideration when choosing the ART regimen. Based on the available evidence, we believe that low-grade AEs classified as frequent (>5%) should be investigated by proactively questioning the patient in routine clinical follow-up visits. If such AEs are detected, possible alternative causes should be explored. If no other reasons are found, and if they are associated temporally with exposure to a given drug, a change in treatment should be assessed. This procedure is also recommended when mild but persistent AEs are reported, as these may considerably deteriorate a patient's QoL and eventually compromise treatment adherence.

## Bone toxicity

### Current status

In Spain, the prevalence of bone disease in subjects with HIV infection is 2.8%.<sup>78</sup> Importantly, HIV infection is associated with an increased risk of fractures.<sup>79</sup> In PLWH, the risks of any fracture and a fragility fracture are increased 1.5-fold, whereas the risk of a hip fracture is increased 4-fold compared with uninfected controls.<sup>80</sup> Regarding specific treatments, it has been demonstrated that subjects treated with tenofovir disoproxil fumarate lose significantly more bone mineral density (BMD) than those treated with tenofovir alafenamide or abacavir or regimens not containing any of them, and have worse bone architecture and quality.<sup>81</sup> Tenofovir disoproxil fumarate is also associated with secondary hyperparathyroidism, phosphaturia and significant alterations in biomarkers of bone metabolism.<sup>19–22</sup> Differences are magnified when tenofovir disoproxil fumarate is combined with boosted ART regimens. Despite these negative effects, in terms of symptomatic severe clinical toxicity, no differences in G3/4 AEs, severe AEs, bone-related fractures or discontinuities have been observed with or without tenofovir disoproxil fumarate in randomized clinical trials, probably due to the low frequency of these events in young subjects.<sup>20,82</sup>

### Areas for improvement

An evaluation of baseline BMD is advisable in postmenopausal women, individuals with bone disease or factors associated with an increased risk of osteoporosis, fracture risk assessment tool (FRAX) score >10%, or age ≥50 years, and all patients treated with tenofovir disoproxil fumarate. Furthermore, the use of tenofovir disoproxil fumarate should be avoided in subjects with or at risk of developing osteopenia or osteoporosis.

## Renal toxicity

In Spain, the prevalence of renal disease in people with HIV infection is 5.9%.<sup>78</sup> Among HIV-positive individuals in North America, chronic kidney disease (CKD) incidence increases by 11-fold among those aged 60–69 years old compared with those aged 40 years old. Moreover, the CKD incidence rate remains disproportionately higher in blacks versus non-blacks.<sup>83</sup> In two systematic reviews including 14<sup>81</sup> and 25<sup>82</sup> studies, tenofovir disoproxil fumarate was associated significantly with mitochondrial toxicity-mediated renal tubular dysfunction, and more rarely, with tubular and glomerular damage, processes that are not always reversible. Consequently, for the early diagnosis of tenofovir disoproxil fumarate-associated renal effects and to allow for recovery after drug withdrawal, a systematic routine monitoring of glomerular and tubular renal function is continuously required.<sup>84</sup> On the other hand, treatment with tenofovir disoproxil fumarate, albeit highly infrequently, has also been related with higher rates of Fanconi syndrome and therapy discontinuations due to renal AEs.<sup>81</sup> In terms of severe renal toxicity, no differences have been demonstrated between tenofovir disoproxil fumarate and tenofovir alafenamide in unboosted regimens (without /cobicistat and /ritonavir).<sup>78</sup> However, higher treatment discontinuation rates have been observed with tenofovir disoproxil fumarate in boosted regimens.<sup>85,86</sup> Finally, given the low number of events, no differences in severe renal toxicity have been demonstrated between



tenofovir disoproxil fumarate and a comparator without tenofovir disoproxil fumarate with unboosted regimens.

### Areas for improvement

In boosted regimens, and if tenofovir is to be included, the use of tenofovir alafenamide is preferable to tenofovir disoproxil fumarate because of its clinical renal safety profile. In subjects with any kind of renal disease or with a higher risk of developing it [ $\geq 50$  years of age, arterial hypertension, type II diabetes mellitus, receiving potentially nephrotoxic drugs, estimated glomerular filtration rates (eGFR)  $\leq 60$  mL/min (or  $>60$  mL but progressively decreasing), urine protein:creatinine (UP/C)  $>50$  mg/mmol], the use of tenofovir disoproxil fumarate should be specifically avoided. In contrast, the use of tenofovir alafenamide, abacavir or dual regimens with dolutegravir (dolutegravir/lamivudine or dolutegravir/rilpivirine) does not require systematic monitoring of renal (glomerular and tubular) toxicity, so resource consumption and the need for bi-annual urine collection in routine visits can be avoided.

## Cardiovascular risk

### Current status

In Spain, the prevalence of cardiovascular disease (CVD) in subjects with HIV infection is 4.7%.<sup>78</sup> A model based on the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort showed that the median age of people with HIV on ART will increase from 43.9 years in 2010 to 56.5 years in 2030, by which time 78% of people with HIV will have been diagnosed with CVD. The increase in RR of myocardial infarction among people with HIV ranges from 20% to 100%, compared with people without HIV.<sup>87</sup>

Controversy currently surrounds a possible increase in CVD in HIV-infected subjects without other associated comorbidities and not exposed to toxic antiretroviral drugs (not in current use). Heart failure, sudden death and stroke are clearly the cardiovascular events with the greatest incremental risk in PLWH.<sup>88</sup> More controversial, however, are the increased rates of acute myocardial infarction (AMI) and pulmonary hypertension observed in some studies.<sup>89,90</sup> To date, no ART currently recommended for initiation or switch has been associated with a higher risk of arterial hypertension.<sup>91</sup> Drugs showing a good metabolic profile include some NNRTIs (rilpivirine) and all INIs. Specifically, the metabolic profile of darunavir is no worse in terms of risk of insulin resistance, arterial hypertension, diabetes or weight gain, although a worse lipid profile has been confirmed,<sup>20,92,93</sup> while data on its association with AMI are conflicting.<sup>93</sup>

In subjects aged 40–75 years without type II diabetes mellitus and with a 10 year cardiovascular risk of 7.5%–19.9% (intermediate risk), the presence of HIV infection as a chronic inflammatory condition is a factor for increased cardiovascular risk, so the addition of statins is recommended. This recommendation could even be extended to subjects at 5%–7.5% risk (borderline risk) who have chronic kidney disease or hypertriglyceridaemia ( $>175$  mg/dL).<sup>93</sup>

Specifically, an association between abacavir use and increased risk of AMI has been suggested. However, results from both meta-analyses of randomized clinical trials and cohort observational studies have been inconclusive.<sup>89,94</sup> No recommendations from drug regulatory agencies in this respect have been included in the summary of product characteristics. However, most guidelines

recommend avoidance or caution with abacavir in subjects with intermediate or elevated CVD risk. The new IAS-USA ART guidelines have removed the combination dolutegravir/abacavir/lamivudine as a preferred regimen for this reason.<sup>22</sup> Additionally, subjects with high CVD risk usually have a simultaneously higher risk of toxicity or renal affectation.<sup>89,94</sup> Importantly, when considering the possible increased risk of AMI/CVD with abacavir and the confirmed risk of renal or bone toxicity with tenofovir disoproxil fumarate, tenofovir alafenamide and the two-drug regimens without abacavir or tenofovir disoproxil fumarate may stand out as favourable options, as they are not associated with any of these potential risks.

Another relevant factor when assessing cardiovascular risk is smoking, which is responsible for 20% of cardiovascular deaths in the general population of the USA.<sup>90,93,95</sup> Importantly, smoking is the most important factor for increased cardiovascular risk in PLWH, in whom smoking rates are 2–3 times higher than in non-HIV infected individuals.<sup>96,97</sup> In heavy smokers, smoking cessation is associated with a significant reduction in the incidence of cardiovascular events at 5 years [ $-4.51$  cases/1000 subjects (95% CI  $-5.90$  to  $-2.77$ )], although even then, the risk remains higher than that of non-smokers even beyond 5 years after quitting. The increased risk completely disappears 10–15 years after quitting.<sup>90,93,95</sup>

### Areas for improvement

All patients should be encouraged to lead a healthy lifestyle (diet and physical exercise). Regular monitoring of blood pressure should be performed at 6 monthly visits, and optimal treatment for arterial hypertension, hyperlipidaemia, antiplatelet aggregation and type II diabetes mellitus should be prescribed when required. In subjects with a 10 year risk of CVD of  $\geq 10\%$ , a change in ART to an appropriate regimen, including NNRTIs (rilpivirine or doravirine) or non-boosted INSTIs is recommended, if possible. Furthermore, abacavir should be avoided in subjects with moderate or high cardiovascular risk. Based on the available evidence, we believe that the comprehensive care of HIV-infected individuals should also include systematic screening for smoking, access to smoking cessation programmes and detection of subsequent relapses.

## Weight gain and obesity

Obesity is a multifactorial disease that affects individuals the world over, regardless of sex, race, age, racial condition or geography.<sup>98</sup> Consequently, weight gain and obesity are also important aspects to be assessed in patients receiving ART. In white subjects aged 35–50 years, the average weight gain in 1 year is about 0.5–1 kg.<sup>99,100</sup> Sufficient evidence is available from cohort studies and randomized clinical trials to conclude that bicitegravir, dolutegravir and tenofovir alafenamide are associated with significantly higher increases in weight, abdominal girth, obesity rates (BMI  $\geq 30$  kg/m<sup>2</sup>) and metabolic syndrome than efavirenz.<sup>51,72,101</sup> Rilpivirine and darunavir appear to be associated with smaller increases in weight. On the other hand, black race and female sex increase this risk of weight gain and metabolic syndrome, and the sum of different factors has an additive or synergistic effect on weight gain and obesity rates.<sup>72,99–101</sup> It is important to emphasize that we are

talking here about a classic obesity metabolic syndrome, rather than the fat redistribution associated with lipodystrophy, the underlying mechanisms of which are entirely distinct and still poorly understood.<sup>72,99–101</sup>

Efavirenz has been associated with weight loss in many trials and tenofovir disoproxil fumarate shows a protective effect against weight gain. The trials studying a switch from tenofovir disoproxil fumarate to tenofovir alafenamide suggest that most of the difference is due to stopping tenofovir disoproxil fumarate rather than starting tenofovir alafenamide.<sup>102</sup>

The scenario in treatment-naïve subjects with low CD4 counts and a high plasma HIV-RNA is different. Most of these individuals have lost weight due to HIV-associated wasting and show a return to health associated with weight recovery in the first year of treatment.

To date, no data have been obtained from randomized clinical trials to support a specific switch regimen in the case of excessive weight gain or to suggest that obesity should be considered when choosing initiation ART.

### *Areas for improvement*

Despite the lack of convincing data on the impact of specific drug regimens on weight gain and obesity metabolic syndrome, there is enough evidence pointing to body weight and BMI as relevant concerns in PLWH, at least in some populations with special risk. Consequently, we believe that they should be monitored at every 6 month visit. In individuals with a significantly greater weight gain than expected, not justified by other causes and associated over time with exposure to a given ART, the possibility of changing to a regimen that does not include these drugs should be considered. In obese individuals, dietary intervention and structured exercise should be recommended.

## **Non-alcoholic fatty liver disease (NAFLD)**

### *Current status*

In the general US population, NAFLD is associated with 8% of overall mortality and up to one-third of the mortality associated with diabetes and liver disease.<sup>103–106</sup> Non-alcoholic steatohepatitis (NASH) is currently the most increasing cause of liver transplantation and its impact is going to be crucial as well for PLWH, particularly once HCV is going to be cured.<sup>107,108</sup> NAFLD is common in people with HIV infection (30%–40%); it is associated with overweight/obesity (BMI 25–30/>30 kg/m<sup>2</sup>), diabetes mellitus and lipodystrophy and usually appears in the context of a metabolic syndrome.<sup>103–106</sup> There is also an association between liver steatosis and a worsening lipid profile. NAFLD is diagnosed by imaging techniques, such as liver elastography with controlled attenuation parameter (CAP) measurement, ultrasound and MRI, all of which can differentiate hepatic fibrosis from steatosis. Some scores constructed from liver biomarkers that show acceptable diagnostic certainty are also available. Finally, in advanced stages (NASH), liver biopsy may be required to confirm the diagnosis.<sup>103–106</sup> Many new treatment strategies with a wide array of mechanisms are being assessed in Phase 2–3 studies and are expected to be implemented soon in the field.

### *Areas for improvement*

NAFLD in HIV-infected subjects should be actively assessed, especially in the presence of obesity, diabetes mellitus and lipodystrophy. For HIV patients with NAFLD, metabolic-neutral ART schemes should be administered. Fibrosis stage  $\geq$ F2 may require specific treatment, a topic that is being very actively investigated at present. Optimal control of the lipid profile is recommended.

## **Psychiatric disorders and HIV**

### *Current status*

Psychiatric disorders are common in subjects with HIV infection (20%–40%), especially in women, in whom the incidence (30%–60%) is higher than in the general population (5%–10%).<sup>109,110</sup> Although depression and anxiety are the most frequent conditions, addictive disorders, dual pathology, psychosis/schizophrenia, bipolar disorder and sleep disorders are also prevalent.<sup>109,110</sup> Some of these disorders can be associated with exposure to certain drugs, causing deterioration of the patient's QoL, which may subsequently lead to compromised ART adherence.<sup>109,110</sup> It is worth stressing that these disorders are often under-diagnosed, especially those of lower intensity, including low-degree ART-related neuropsychiatric AEs, which the patient may attribute to other causes.<sup>109,110</sup>

### *Areas for improvement*

Given the prevalence of psychiatric disorders among HIV patients and their impact on their QoL and on therapeutic success, active surveillance should be maintained to detect possible symptoms, assess treatment suitability and, when present, evaluate their putative relationship with exposure to drugs, including ART. External causes should be also evaluated. When symptoms are determined to be 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 assessed, as in most instances the effect is reversible upon discontinuation of the drug.

## **Sexual dysfunction and HIV**

### *Current status*

Sexual dysfunction is not uncommon in subjects with HIV and includes loss of desire or libido, impotence (up to 40% of men with HIV) and orgasmic disorders.<sup>111</sup> It is important to differentiate the unmet needs according to men and women, as they are different and it is a problem that is not easy to come. However, targeted questions are often required for detection of such problems. When detected, hypogonadism, peripheral artery disease and psychological causes (anxiety, stigma) should be specifically ruled out, and the appearance of sexual dysfunction as a potential pharmacological adverse effect must be considered (especially with PIs).<sup>111,112</sup> A temporal association with treatment should be evaluated after ruling out organic or functional causes, and prescription of phosphodiesterase-5 inhibitors (sildenafil and its derivatives) must be considered.

### Areas for improvement

The presence of sexual dysfunction should be proactively assessed. After ruling out organic causes or psychological factors, an adverse pharmacological effect must be considered. If sexual dysfunction is temporarily associated with the administration of a drug and organic/psychological causes have been ruled out, the possibility of switching to a safer alternative is recommended. If indicated, phosphodiesterase-5 inhibitors should be prescribed for men with impotence, smoking cessation should be encouraged, and blood pressure and diabetes control optimized.

### Pharmacokinetic interactions

Potential DDIs occur with up to 40% of regimens that include pharmacokinetic enhancers (cobicistat or ritonavir) and PIs or elvitegravir. These interactions are reduced up to 14% with rilpivirine and up to 8% with regimens that include dolutegravir, raltegravir or bictegravir.<sup>113–116</sup> Nevertheless, potentially serious interactions or those requiring intervention are rare (<5%). Drugs metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or glucuronidation will have fewer interactions with cobicistat than with ritonavir.<sup>113–116</sup>

Polypharmacy (defined as taking at least five drugs) is more common among older subjects than in younger ones (17%), and is associated with increased morbidity and mortality and a greater risk of pharmacokinetic interactions. Importantly, older HIV-positive individuals use higher numbers of non-ART drugs (4.7%) than individuals without HIV.<sup>113,116</sup> Psychotropic drugs, drugs for metabolic diseases and CVD medications are among the most commonly consumed families of non-antiretroviral drugs.<sup>113,116</sup>

In addition, the practice of chemsex is common among some patients with HIV, and involves potential DDI-associated risks. Thus, an increased DDI risk exists with gamma-hydroxybutyrate (GHB), ketamine, sildenafil (tadalafil, vardenafil) and benzodiazepines (midazolam, triazolam), and a more limited risk with ecstasy (MDMA), metabolized by CYP2D6. However, the therapeutic index of the latter is narrow, making it potentially dangerous.<sup>117</sup> On the other hand, although mephedrone and methamphetamine (metabolized by CYP2D6) have a low DDI risk, major changes induced by small interactions can be clinically relevant, because their pharmacokinetics are not linear. A mild/moderate interaction exists with cocaine.<sup>117</sup> Finally, it is worth noting that, in the scenario of chemsex use, there is no rigorous control of product composition, dosages or the magnitude of occasional consumption.<sup>117</sup> Furthermore, these substances are usually consumed with alcohol. The use of chemsex can be difficult to detect in routine HIV follow-up visits because it is often inadequately addressed by clinicians or because of patient concealment. There is a significant association between chemsex use and the presence of sexually transmitted infections (STIs), particularly in MSM because of the coexistence of high-risk behaviours that facilitate both.<sup>118,119</sup> Young age, searching for sexual contacts on the internet and exchanging sex for money significantly increase risk.<sup>118,119</sup>

### Areas for improvement

If possible, when efficacy and safety profiles are the same, a regimen with a lower DDI potential, specifically not including pharmacokinetic enhancers, are preferred.

Because of the risk of potential DDIs, subjects practising chemsex should not receive a boosted regimen including cobicistat or ritonavir if other alternatives are available. A regimen with a long half-life and a long forgiveness period, which makes therapeutic failure difficult in case of occasional ART forgetfulness (e.g. at weekends) is recommended. The available data suggest that MSM diagnosed with repeat STIs use chemsex significantly more frequently. Consequently, they should not receive a boosted regimen including cobicistat or ritonavir if there is an equally safe alternative with a more favourable interaction profile, even if the use of chemsex has not been captured in the follow-up, because of the significant association with even occasional use of chemsex and the risk of developing DDIs.

## QoL

### General aspects

#### Current status

In 2016, the Global Health Sector Strategy on HIV adopted by the WHO established the '90–90–90' target, calling on health systems to aim for an HIV diagnosis rate of 90%, 90% of diagnosed patients on treatment and 90% of treated subjects achieving viral suppression for 2016–21.<sup>120</sup> The WHO roadmap towards 'taking HIV infection out of isolation' included the following milestones.<sup>120</sup>

- Mortality: to reduce HIV-related deaths to <500 000/year.
- Diagnosis and treatment: reaching '90–90–90' target by 2021.
- Prevention: to reduce new HIV infections to <500 000/year.
- Discrimination: to eliminate laws, regulations or policies that discriminate against people with HIV, especially in the health-care setting.
- Financial sustainability: to cover 95% of the financial needs of countries with limited resources to address the epidemic, and an international investment of at least \$12.7 billion per year in such countries.
- Innovation: to increase research into new drugs and vaccines and to provide access to integrated health services to fight HIV, TB infection, HBV infection, HCV infection and STIs in 90% of countries.

The same year, based on the available evidence demonstrating that PLWH who have achieved viral suppression still must contend with other intense challenges negatively impacting their QoL, Lazarus *et al.*<sup>121</sup> proposed adding a 'fourth 90' to the testing and treatment target set by the WHO. That is, to ensure that 90% of people with viral load suppression have good health-related quality of life (HRQoL). Since HIV infection has become a chronic disease with a similar life expectancy to that of the general population, achieving this target must also be considered of utmost importance. Consequently, to meet the needs of PLWH, health systems must become more integrated and patient centred. Additionally, once ART has reached high efficacy and durability levels, it should also ensure a good QoL through a greater simplicity, better tolerability and reduced toxicity. The WHO has established a new target for 2030: 95% diagnosed, 95% on treatment, 95% achieving viral suppression.<sup>122</sup> According to the previous proposal of Lazarus *et al.*,<sup>121</sup> and considering that, as we suggest, patient QoL should be included in the redefinition of

the therapeutic success concept, we believe that a rate of 95% of individuals with good HRQoL should be also achieved by 2030.

### Areas for improvement

When managing people with HIV, greater emphasis must be placed on comprehensive healthcare, to ensure that patients have a better QoL and that they are free from stigma and discrimination. Strategies addressed specifically at improving this QoL should be implemented in HIV care programmes. ART should contribute to this by being simpler, better tolerated and less toxic. Finally, there is a need of more research on QoL based on the different settings and geographical scenarios.

### HRQoL and patient-reported outcomes (PROs)

#### Current status

HRQoL in HIV infection depends partially on the patient's ART regimen. In double-blind randomized clinical trials, the impact of medical treatment is assessed using PROs, a tool that can evaluate the patients' perspective, by way of specific questionnaires that are administered '*ad hoc*' and validated for a specific disease or condition.<sup>123</sup> These questionnaires usually include other variables (psychological, social, lifestyle, etc.) that influence the patient's wellbeing and performance, but which are not easily captured in a standard medical appointment.<sup>123</sup> PROs can be evaluated using a variety of tools adapted to different scenarios. Thus, they can be measured in absolute terms, such as the severity of a symptom or sign, or the change from a previous measurement.<sup>124</sup> They can also be one-dimensional or multi-dimensional. Several questionnaires can assess the patient's QoL in a general way, including the Pittsburgh Sleep Quality Index, the EuroQoL-5D (EQ-5D), the 12-Item Short Form Health Survey (SF-12), the 20-Item Short Form Health Survey (SF-20) and the 36-Item Short Form Health Survey (SF-36). More specifically, the King's College 'Positive Outcomes',<sup>125</sup> the HIV Symptom Index (HIV-SI), the WHO Quality of Life in HIV-infected Persons instrument (WHOQOL-HIV), the HIV-QoL and the Patient Reported Outcomes Quality of Life-HIV (PROQOL-HIV)<sup>126</sup> are used for HIV patients.

PROs provide key data on the patient's perception of their health and treatment. These data can only be obtained by specifically asking the patient, because they involve symptoms that are not usually obvious to the observer, such as tiredness or headaches, or psychological symptoms (anxiety or depression), or those that occur when the observer is not present (i.e. lack of sleep).<sup>124,127-130</sup> PROs are emerging as one of the key areas for exploring HIV infection as a chronic disease with an almost normal life expectancy.<sup>125,131-134</sup> The maintenance of both long-term physical and mental health is considered the main challenge for HIV medicine, but these variables can be missed by health professionals in busy appointments. Thus, the routine use of PROs may help to identify patients' problems and concerns and improve their progress by revealing and managing these issues.

To date, the best tools for measuring HRQoL in people with HIV are not yet defined. In a review of systematic reviews, nine generic and seven HIV-specific questionnaires were analysed. For inclusion, these tools had to be able to be administered within 10 min and cover at least three domains (physical, social and mental/emotional).<sup>123</sup> The Medical Outcomes Study HIV Health Survey

(MOS-HIV), the WHOQOL-HIV-BREF and the PROQOL-HIV showed the best results. However, these questionnaires need to be validated and adapted to each country and language. Recently, a cross-sectional study aimed at validating the WHOQOL-HIV-BREF questionnaire was carried out in 1462 people with HIV from 33 centres in Spain.<sup>135</sup> Among the factors associated with poorer HRQoL, female sex, heterosexual condition, low cultural and socioeconomic level, infection through drug use, age >50 years and a longer infection period after diagnosis were identified.

### Areas for improvement

Care for people with HIV should include an assessment of their HRQoL. The use of PROs, although difficult to incorporate into clinical practice, can help to identify patients' problems and concerns with ART, and can contribute to improving their progress.

Ideally, tools for measuring QoL in people with HIV should be those that can be performed within a reasonable time, explore at least the physical, social and mental/emotional domains and have been validated in people with HIV, and, preferentially, in every geographic context and language. In Spain, the WHOQOL-HIV-BREF questionnaire has been validated and meets the criteria described above and, consequently, we believe that it is the most suitable tool currently available. Finally, we think that developing actions to correct the lower-scoring HRQoL factors detected when applying these tools should be a priority.

### PROs in clinical trials

#### Current status

The inclusion of PROs in HIV clinical trials is not a recent phenomenon. Thus, in the 073 study, conducted in patients who were virologically suppressed after switching to an efavirenz/emtricitabine/tenofovir disoproxil fumarate STR, the impact of the switch on the CNS was evaluated using a questionnaire for the first time.<sup>136</sup> More recently, the PRO-STR study, conducted in subjects who switched to an efavirenz/emtricitabine/tenofovir disoproxil fumarate STR, assessed the proportion of patients who reported any symptom at baseline and/or during follow-up, using the AIDS Clinical Trials Group (ACTG)-HIV Symptom Index.<sup>137</sup> Similar studies have been conducted in patients who have switched to INSTI-based regimens, such as that of Raffi *et al.*,<sup>138</sup> in which PROs were recorded, with particular attention being paid to neuropsychiatric symptoms. PROs have their greatest value when performed in double-blind clinical trials. The influence of the treating physician in open-label studies can introduce a significant bias in the results. The most recent data come from the 1489 and 1844 studies, assessing the efficacy and safety of bicitgravir/emtricitabine/tenofovir alafenamide versus dolutegravir/abacavir/lamivudine in naive and pre-treated patients, respectively.<sup>48,49,67</sup> Bicitgravir/emtricitabine/tenofovir alafenamide efficacy was non-inferior and this regimen resulted in less drug-related AEs than those based on dolutegravir. It is worth mentioning that abacavir/lamivudine-containing regimens have been associated with a higher incidence of nausea than emtricitabine/tenofovir disoproxil fumarate,<sup>139</sup> while dolutegravir has been associated with neuropsychiatric-related AEs in some cohorts, although these results are controversial.<sup>140-146</sup> In both the 1489 and 1844 studies, specific (HIV-SI) and general questionnaires [SF-36, Pittsburgh Sleep Quality Index, Work

Productivity and Activity Impairment General Questionnaire (WPAI)] were performed to assess participants' QoL after switching. In the case of HIV-SI, patients had to report whether they had a total of 20 different symptoms and, if so, they were asked to score the degree of discomfort/importance on a scale of 0 to 4.<sup>147,148</sup> The validated Pittsburgh Sleep Quality Index questionnaire consists of 19 items exploring seven different domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, possible sleep disturbances (e.g. waking up at night), use of hypnotic medication, and daytime dysfunction. In the 1489 and 1844 studies, PROs were found to significantly favour bictegravir/tenofovir alafenamide/emtricitabine over dolutegravir/abacavir/lamivudine when initiating or changing treatment.<sup>147,148</sup>

### Areas for improvement

Based on the available evidence, the application of PRO questionnaires in double-blind randomized clinical trials of new ART is advisable, especially in scenarios of equality in terms of efficacy and safety, as they may serve to discriminate between different treatment options. Questionnaires validated for HIV infection should be used, preferably validated for the geographical context in which they have been developed.

## Use of electronic tools in HRQoL research in PLWH

### Current status

In a systematic review of 13 randomized clinical trials and one open-label study analysing the use of electronic tools in patients with chronic conditions to detect drug-related AEs, significant increases in medication switches to correct side effects were observed, and in more than half, symptoms improved after medication changes.<sup>149</sup> Moreover, most patients found these tools useful for improving their communication with their caregivers and had better results in health-related PROs than those who did not use them.<sup>149</sup> Importantly, as Fredericksen *et al.*<sup>150</sup> demonstrated in a study conducted in several clinics in the USA, care providers view these types of electronic tool favourably, as long as they are adapted to be clinically relevant in the monitoring of their population, are well integrated in the clinical management and are easy to interpret. All of these approaches facilitate the detection of the main problems of patients and how they change over time. It is essential that these tools are adapted to the target population, and that they are easily accessible and understandable.<sup>151</sup>

### Areas for improvement

Electronic tools (devices, websites, applications) that may facilitate PRO research and contribute to improving the QoL of patients are currently available. These tools should be adapted to each population, well integrated into clinical management and easily accessible and understandable.

## QoL and HIV-associated stigma

### Current status

Stigma and discrimination are major obstacles to good QoL in PLWH. Stigma is a huge problem among PLWH with many consequences (late testing, less adherence and retention on care).

Despite considerable efforts to combat HIV-related stigma, patients' personal experiences are inadequately assessed and documented, and few effective interventions have been found. There are few well-designed intervention studies that document stigma reduction. Indeed, to date, few projects involve PLWH in their design and implementation, despite the already demonstrated relevance of this fact on their impact and sustainability.<sup>152</sup> Furthermore, evidence of methods to reduce stigma in key populations and in many geographical contexts is scarce. There is a lack of knowledge about how to address stigma in populations disproportionately affected by HIV and how to prevent discrimination in healthcare settings outside of HIV-specific care, which impedes greater access to management of psychiatric disorders and comorbidities.<sup>152</sup> Consequently, stigma management and reduction presently lags behind scientific advances in HIV infection.

The possibility of HIV transmission has been and continues to be one of the factors causing and contributing to increased stigma, and that negatively impacts on self-stigma. Evidence from recent randomized clinical trials and cohorts showing that sustained undetectability is associated with lack of HIV transmissibility has helped to reduce this cause of self-stigma.<sup>41</sup> However, despite strong evidence of the absence of sexual transmission of HIV with undetectable plasma HIV viral load, we are continuing to experience all-time peaks in the rates of sexually transmitted diseases such as *Chlamydia*, syphilis and gonorrhoea. Therefore, promotion of safe sexual practices must continue also in patients with suppressed HIV viraemia.

### Areas for improvement

Because stigma remains a major problem for PLWH, the inclusion of measures to assess it and to evaluate its impact on the patient's QoL is recommended. The patient, the healthcare setting, support groups and the general population should be targets for the reduction of HIV-related stigma.

Regarding HIV transmission, people with HIV on ART should be properly informed that once they reach undetectable PVL and maintain it for more than 6 months, and if treatment adherence is appropriate, virus transmission through sex is highly unlikely. Although not one single case of HIV transmission has been described from a patient with undetectable viral load, continued treatment adherence is of paramount importance in this scenario. Despite the evidence that U=U, national guidelines still recommend taking appropriate precautions to prevent sexual transmission. All of this information will help to reduce a factor that generates significant self-stigma.

## Conclusions and future perspectives

Nowadays, in countries with universal access to ART and without resource limitations, PLWH are mostly stable and enjoying a normal life. Still, they are not free of suffering many complications that affect their HRQoL, mainly related to ageing, emergent comorbidities or, in some cases, because of AEs related to ART.

This change of scenery must be considered to achieve the best HRQoL possible for our patients. In that line, our model of care should be adapted to a multidisciplinary approach. This may be reached in different ways depending on the place where care is delivered. In some cases, different professionals, including mental

health professionals and/or nutritional advisors, could be included in the care team, whereas in other cases, the patient should have an easy referral to these professionals. In any case, the ID/HIV physician should be the coordinator of the whole attention. The final aim is that every patient has access to personalized care, focusing on his/her individual problems in contrast to homogeneous attention for all patients. In other words, stratification should be made to deliver every patient tailored interventions while maintaining the main objectives of sustained virological suppression, immunological recovery and absence of opportunistic diseases. In this context, the use of PROs must be somehow introduced to detect and correct patients' problems and worries that otherwise will be missed.

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