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ABSTRACT

The term "HIV controller refers to the small proportion of HIV-infected individuals who are able to spontaneously control viremia at very low levels. One major unresolved question is whether controllers should receive antiretroviral therapy (ART), given that the international guidelines recommend treatment for all HIV-infected individuals. Differences in the definitions of a controller (in terms of the viral load cut-off and the duration of viral control) and contrasting reports on CD4 T cell decline, chronic immune activation, the cardiovascular risk, and loss of viral control in controllers have prevented the development of a consensus view. In the present review, we (i) discuss the indications of initiating ART in controllers, (ii) highlight the impact of the various definitions of HIV control, and (iii) emphasize the value of personalized care/patient-centred approaches for controllers.

Introduction

The term "HIV controller" (HIC), or "elite controller" (EC) refers to the very small proportion (<1%) of persons living with HIV (PLWH) who have never received antiretroviral therapy (ART) but have been able to spontaneously keep their plasma HIV-1 RNA load below quantifiable levels for at least several years (1,2). HIV control is favoured by protective MHC alleles, and is probably achieved through the combination of several different mechanisms - including the development of effective CD4+ and CD8+ T cell responses, and the relative resistance of the person's CD4+ T cells and macrophages to HIV infection (3–5). A better understanding of these mechanisms is important for HIV remission strategies, and several international efforts are now focused on this issue.

The present article reviews the opportuneness of initiating ART treatment in controllers.

The various international guidelines recommend the very early initiation of ART in all HIV-infected people, in order to limit viral spreading, the constitution of an HIV reservoir, early gut/mucosal damage, excessive immune activation, and the risk of transmission (6,7). Interestingly, some international guidelines devote a chapter to controllers, whereas others feature a single sentence (Supplemental Table 1). Data on controllers are scarce, and although ART is recommended, its initiation can perhaps be delayed if close follow-up is possible. While some experts argue strongly for the implementation of ART in all controllers, others prefer a case-by-case approach.

Here, we review the state of the art in this respect, and suggest several strategies for evaluating whether and how controllers should receive ART.

How is a controller defined?

In the literature, the definition of a controller often differs from one study to another (8) with regard to the viral load (VL) cut-off (ranging from <50 copies (cp)/mL for "elite controllers"

(ECs) to <2000 copies/mL for "viremic controllers") and the duration of control (usually ranging from 3 VLs below the cut-off within 12 months to the last 5 VLs below the cut-off and a documented history of ART-naïve HIV infection for 5 years or more). This definition is of paramount importance, since observations made in controllers with always undetectable VL cannot be extrapolated to "viremic controllers" in whom the risk of non-AIDS events is much higher and is related to a significant decrease in the CD4 T cell count. However, two definitions of a controller are used fairly widely (8): (i) at least two or more VLs below 50 cp/ml during a year in the absence of ART, and (ii) more than 90% of the VLs below 400/500 cp/ml over more than 5 or 10 years.

Each definition has limitations. The first definition may not select extremely long-lasting phenotypes, as it has been shown that up to 26.3% of HIV-infected individuals can spontaneously achieve one VL below the detection threshold; for two consecutive VLs below the threshold, the proportion is 8.5% (9). For the second definition, a patient with all his/her VLs between 50 and 400 cp/ml may still be considered as a controller. Therefore, controllers form a heterogeneous population. All clinical observations in controllers need to be interpreted with caution and must take account of the duration of viral control and the threshold used to define an undetectable VL.

What is the justification for treating controllers?

In addition to recommendations of universal treatment, several clinical situations can trigger the initiation of ART in controllers.

The first is the loss of viral control. Virological progression (defined as a constant increase in viremia) might be associated with the loss of immunological-mediated control or with HIV super-infection. Both have been documented in a few studies and case reports (10,11). An analysis of the European COHERE collaborative group of HIV cohorts revealed that of the 1067 identified controllers (VL cut-off: 500 cp/mL), the probability of losing viral control (defined as

two consecutive VLs>2000 cp/mL) and the probability of initiating ART were respectively 13% and 37% after 6 years (12). Also, the study by the AIDS Healthcare Foundation et al showed that loss of spontaneous viral control (defined by ≥ 3 VL <50 RNA copies/mL within one year in the absence of ART) might be observed at 1.22% per year, and significantly associated with viremia 'blips' (13).

The second situation is persistent, low-level viral replication in controllers - reflected in some cases by intermittently detectable viremia during follow-up. An international study of the characteristics of 140 controllers with a VL cut-off level of 400 cp/mL since seroconversion showed that over one-third experienced blips (i.e. episodes of detectable viremia between periods of undetectability) during follow-up, and that this led to the loss of viral control in 15.7% of the participants (14). Prior to the loss of viral control, the presence of repeated detectable VLs was associated with a progressive decrease in the CD4 T cell count and thus a greater risk of clinical events. The viral replication in tissues (like the gut and the lymph nodes (15,16)) has been documented in some controllers. It might lead to viral production with potential blips, and recirculation of recently infected cells. Different mechanisms might contribute to the maintenance of the HIV reservoir in controllers with also clonally expanded reservoir T cells.

A third reason for initiating ART in controllers might be the need to limit the risk of HIV transmission. So far, only one small study of the presence of HIV RNA and DNA in the semen of controllers has been published (17). In fact, the presence of virus in semen (less than 1000 RNA copies/mL in 4 of the 10 analyzed controllers) was correlated with the simultaneous detection of plasma HIV viremia. It is not known whether the viral levels detected in the semen are enough to transmit infection. However, it is recognized that "u=u" (undetectable patients being untransmissible) and historical studies strongly suggest that in untreated patients, the threshold

level for transmission might be around 1500 copies/ml (18). Of note, HIV transmission by a controller has never been reported.

A fourth situation that may prompt the initiation of ART in controllers is a decline in the CD4 T cell count. Some controllers display a permanently low CD4 T cell count, however. In the French Codex cohort, 3% of the CD4 T cell counts were below 350/ μL, and 14% were below 500/ μL (Lambotte et al, unpublished data). Furthermore, a skewed CD4/CD8 ratio has been highlighted as a reliable predictive marker of non-AIDS-defining events in PLWHs (19). A risk of immunological progression (i.e. progressive CD4 T cell loss) has also been evidenced in many controller cohorts (20–23). The loss of CD4+ T cells has been linked to viral blips and/or persistent, low-level viral replication (20,21,23,24).

Besides immunologic or virologic "progression", the fifth reason for initiating ART in controllers is related to the presence or development of clinical comorbidities. The question is whether controllers have a greater risk of non-AIDS-defining events (nADEs, such as cardiovascular disease or cancer) than non-infected subjects or PLWH on ART. Again, the answer probably depends on the definition of the study population.

The occurrence of cancers has been reported in controllers (25,26). While the incidence might not be easily estimated, the types of cancers resembles those in ART-treated patients and also the general population. Cancer treatments might impact the antiviral immune system, weaken viral control, and lead to flares in the HIV VL, whereas prior or concomitant ART may prevent the latter (24–26).

Some studies have analysed the risk of nADEs in different cohorts of controllers (27–32) (summarized in Table 1). Crowell et al. studied 149 "elite" controllers and reported that they were at a greater risk of all-cause hospitalizations (especially, hospitalizations for psychiatric

and cardiovascular diseases), relative to PLWH on ART (29). The increase in cardiovascular risk had been previously indicated by studies showing that controllers had a greater carotid artery intima media thickness (33) and more coronary artery calcification (34) than HIV-negative controls. One hypothesis to explain this striking observation could be that controllers are less frequently seen and might miss opportunities to detect and treat comorbidities. A second study by the same group (focused on a younger population of US veterans, with a lower incidence of HCV co-infection (6%)) did not find an elevated risk of hospitalization in 221 controllers (including 33 "elite" and 188 "viremic") (30), and in the French cohort, very few cardiac and vascular events were observed in controllers (32). In the Spanish controller cohort, Lucero et al reported nADEs in viremic controllers (n=76) but not in controller with undetectable viremias (n=64) (27). These findings have been confirmed in a second study of a Spanish cohort including 138 "elite" and 182 "viremic" controllers, experiencing less nADEs as compared with ART-controlled patients (28). Overall, the main factors associated with occurrence of nADEs in controllers were: the "viremic" controller phenotype, sometimes the CD4 T cell nadir (22), and a strong role for age (29,30). Interestingly, the presence of HCV co-infection has often been related to more complications in population of controllers with higher HCV prevalence (28,29,31).

The last indication for ART initiation in controllers may be persistent, excessive immune activation because this is associated with a poor outcome in PLWH (35).

Many studies have reported higher levels of T cell activation in controllers than in non-infected individuals (36,37). In several cohorts, the loss of CD4 T cells was also associated with immune activation and microbial translocation (36–39). Accordingly, higher levels of immune activation and inflammation appear to be a major determinant of progression in controllers (24,39–41). . These data point to a clear role of chronic immune activation in the decline in CD4+ T cell counts observed in some controllers - even when viremia is not repeatedly detected.

However, the findings on immune activation vary from one controller cohort to another (21,42–45). Once again, this reflects the heterogeneity of the "controller" populations depending on the definition used. Also, it is difficult to recommend the use of immune activation parameters as a determining factor for ART introduction since no threshold exist and that these biomarkers are not available in routine clinical care.

Lastly, it is interesting to note that the situations described above are often interrelated. For example, an elevated risk of viral escape is found in controllers showing transient blips during follow-up. Low-level viral replication is also often accompanied by the loss of CD4+ T cells and an increase in immune activation and chronic inflammation (24,41).

What is the impact of ART on controllers?

The large number of publications on the immunological, virological and genetic characteristics of controllers contrasts with the small body of data on their clinical profiles, and the possible benefits of ART in this population.

The international guidelines suggest that ART of controllers could be deferred (relative to other PLWH) and, if initiated, should be thoroughly discussed with the patient (7). Practices in this setting vary from country to country, and the effects of ART in controllers have rarely been assessed (for a summary, see Table 2).

In 2009, Okulicz et al. first reported on ART initiation in 62 controllers from the US cohort of veterans (46). ART was prescribed on a usual-care (i.e. non-standardized) basis. The researchers observed a significant overall increase in CD4 T cell counts. However, this increase was around 50/ µL smaller than that observed in HIV non-controllers. Although the CD4 T cell counts generally increased upon ART initiation in this study, some individuals with low or undetectable VLs before ART experienced CD4 cell count decline - as also observed in a case report (47). Furthermore, the increase in CD4 T cell counts appeared to be lower in controllers with <400

cp/mL VL upon ART initiation vs. HIV non-controllers with VLs between 400 and 9999 cp/mL (mean increase: 34.3/ μL vs. 112/ μL at M6, respectively, and 145/ μL vs. 207/ μL at M24, respectively), whereas the reduction in the VL was similar in controllers and HIV non-controllers. It is noteworthy that some controllers still had a detectable VL after ART, which suggests poor adherence to treatment.

With a view to analyzing the impact of ART on HIV reservoirs (using quantitative co-culture assay), Chun et al. treated four controllers with high CD4+ T cell counts with tenofovir/emtricitabine and raltegravir for 9 months, followed by treatment discontinuation (48). This regimen led to profound decay/depletion of replication-competent HIV reservoirs. In all four patients, the CD4 T cell count and the CD4/CD8 T cell ratio were normal upon ART initiation. The CD4/CD8 T cell ratio increased slightly in all the four patients between treatment M0 and M6, but fell in two of them upon the withdrawal of ART (including one patient with a ratio <1) (49). No relevant effects on inflammatory parameters (such as D-dimer and IL-6 levels) were observed (49).

Hatano et al. studied the effect of 24 weeks of prospective treatment with raltegravir+tenofovir/emtricitabine on 16 asymptomatic controllers (defined by a VL <1000 cp/mL for at least 12 months), including 4 controllers with a VL <40 cp/mL) (50). Changes in T cell counts, immune activation, and RNA and DNA VLs were investigated in blood samples and rectal biopsies. The researchers observed a significant decrease in the plasma and rectal RNA VLs, a significant reduction in the total HIV DNA load in the blood (but not in rectal samples), and a significant overall reduction in the levels of some (but not all) immune activation markers. ART initiation decreased the percentage of activated (HLADR+CD38+) CD4+ and CD8+ T cells in the blood and activated CD8+ T cells in the rectum. Plasma levels of high-sensitivity CRP, IL-6, sCD14 and D-dimers did not fall, and no significant increase in blood or rectal CD4 T cell counts was observed during the short study period.

Boufassa et al. reported retrospectively on the standard-care use of ART in controllers from the French ANRS CO18 cohort, the US SCOPE cohort, the International HIV Controllers study, and the European CASCADE collaboration (51). The 34 enrolled HICs met both the French and the US definitions of viral control (<400 cp/mL for 10 years and <50 cp/mL for 12 months, respectively). The median duration of ART was 15 months, and the median CD4 T cell count at baseline was 268/ µL. Overall, the CD4 T cell count rose significantly but the gain was lower than that observed in viremic non-controllers. This was mostly related to the absence in controllers of the rapid initial increase in CD4 T cell counts (presumably related to CD4+ T cell recirculation) typically observed upon ART initiation in HIV-1-infected individuals. Again, and despite the overall trend, the CD4+ T cell count did not increase in some of the controllers studied.

More recently, Li et al. published the results of the ACTG A5308 study (52). This study enrolled 35 controllers (defined by an RNA VL <500 cp/mL for ≥12 months before ART) having initiated a standardized rilpivirine/emtricitabine/tenofovir disoproxil fumarate regimen (52). The majority (69%) of the controllers had a VL >40 RNA cp/mL at enrolment, and some had a VL of around 1000 cp/mL. The analysis evidenced a significant decline in the percentage of CD38+HLA-DR+CD8+ cells between 24 and 48 weeks after ART initiation and between 72 and 96 weeks. This reduction did not differ between patients with HIV RNA < 40 copies/mL at study entry and the patients with detectable VL, but no data on previous blips were available. ART use was associated with a fall in IP-10 levels but an increase (for unknown reasons) in sCD163 levels. Li et al. emphasized the ART regimen's good safety profile and the patient-reported improvement in quality of life. In contrast, there were no specific effects on the CD4 T cell count (median at entry: 655/µL) or on HIV DNA loads.

In summary, the small available body of literature data confirms that the implementation of ART in controllers is associated with a reduction in the level of viral replication. It appears that ART increases the CD4 T cell count, although the magnitude varies from one individual to another. There appears to be a clear decrease in CD4 and CD8 T cell activation, butthe studies that found

a reduction in the level of immune activation mainly enrolled viremic controllers.. Notably, 97 of the 151 controllers treated with ART in these studies were viremic at the start of the therapy. Moreover, it was not clear that these interventions helped to decrease the size of HIV reservoirs or reduce occurrence of non-AIDS-related comorbidities.

Should we prescribe ART to all controllers?

As emphasized by Gurdasani et al., a thorough review of the literature on clinical outcomes and chronic inflammation in controllers underlined the heterogeneity in the duration of viral control and the VL threshold used in the definition of control. As expected, the outcomes for so-called "viremic controllers" differ from those with undetectable VLs having never experienced any blips (8,53).

We recently described a subset of controllers characterized by the total absence of detectable VLs during follow up (in a routine assay), very low levels of HIV-RNA (in an ultrasensitive assay), and very-low-to-undetectable total HIV DNA loads (also in an ultrasensitive assay). These patients do not experience decreases in their CD4 T cell count or disease progression (53). These patients' HIV-RNA and HIV-DNA loads during the first few years of infection were lower than those of patients who had lost their controller status (54). Other research groups using a stringent definition of controllers have also identified patients with an extreme profile (45,55). We have also observed a negative slope for the HIV DNA load in some controllers (56), which further supports lack of a need for treatment. These results again emphasize the heterogeneity of the controller population. The use of accurate markers of HIV reservoir could be useful to identify controllers with a low risk of progression such as quantitative viral outgrowth assay (57). Hence, with a view to obtaining homogeneous, comparable datasets regarding the risk of "disease progression" and ART implementation, there is an urgent need for internationally accepted, shared, precise definitions or stratifications of controllers.

ART probably does have an important impact on some of the above-mentioned outcomes. The initiation of ART in controllers with low (but detectable) viremia levels currently appears to be important and effective for both HIV control and immune activation. In other cases, we suggest in Table 3 a number of criteria that should be reviewed when ART is questioned for a controller, such as the kinetics of CD4 T cell counts and percentages for patients without persistent detectable viremia but experiencing CD4 T cell decline, and clinical comorbidities or risk factors that might enhance immune activation.

Lastly, one major point to take into consideration is the willingness of controllers to initiate lifelong ART. In their recent paper, Jon Li et al included a majority of patients with pre-ART HIV RNA > 40 copies/mL, since many of the elite controllers (i.e. patients with undetectable VL) "at [their] study sites, even those who had actively participated in research studies for years, were reluctant to begin ART, mostly due to concerns about drug toxicity" (52). Indeed, ART-toxicities exist and, even these therapies are nowadays mostly well tolerated, the potential side-effects might be taken into account in the discussion about the risk-reward ratio to start ART.

Which therapeutic strategies might be studied in controllers requiring treatment?

For controllers needing ART, classical combinations with three drugs are certainly the recommended treatment to be used.

Alongside "classical" combination ART, other therapeutic strategies could be tested in the setting of clinical trials to optimize the risk-reward ratio of the use of ART and their potential adverse events, versus reduction of the frequency of nADEs, or improving the CD4 T cell count. It is the case of dual antiretroviral therapies, long-acting injectable antiretroviral drugs, broadly neutralizing HIV-specific antibodies (58), and/or the use of immunomodulatory strategies (aspirin and statins but also new well-tolerated anti-CMV agents, and new drugs that target

inflammation and immunosenescence), Such strategies might be of particular interest in limiting nADEs and avoiding ART regimens in controllers with an undetectable VL (59,60).

In conclusion, we strongly recommend the adoption of personalized/patient-centred approaches to the treatment of controllers. Learned societies and medical associations should continue to differentiate between well-defined controllers (managed with a "watchful waiting" strategy) and "viremic controllers" (managed accordingly to the general guidelines on ART). Apart from today's conventional ART strategies, innovative ART regimens that are especially suited to individuals with a very low VL could be considered, depending on the individual's HIV control status.

Lastly, there is a need for a collaborative international taskforce in order to better define the controllers to be enrolled in the studies and the endpoints to be considered, such as immune activation mechanisms and clinical comorbidities.

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TABLES

Table 1. Summary of the main studies analyzing non-AIDS defining events in controllers				
Author	Design	Number of patients and definitions	Main conclusions	Main factors as... with nADEs
Lucero et al, 2013 (27)	Prospective cohort study - all nADEs	64 "elite" (HIV VL < LOD during the 1st year FU) 76 "viremic" (LOD<VL<2000 copies/mL during the 1st year FU) 434 noncontrollers without ART. All patients with CD4 T cell counts > 500/μL	Same incidence rate of nADEs in the three groups However, when considering an "elite" phenotype during the entire follow up period, no nADEs was observed.	Age, nadir CD4, coinfection, last detectable
Dominguez-Molina et al, 2016 (28)	Prospective cohort study - all nADEs	138 "elite" (HIV VL < 50 copies/mL during at least one year) 182 "viremic" controllers (50<VL<2000 copies/mL during at least one year), no ART	Lower incidence of nADEs in EC than viremic controllers The incidence of cardiovascular events increased after loss of virologic control.	HCV coinfection duration of follo...
Crowell et al, 2015 (29)	Retrospective cohort study – hospitalizations causes	149 "elite" controllers (≥3 consecutive HIV-1 RNA measurements below LOD spanning ≥12 months) 4709 medical control (same virologic definition but on ART) 7998 "low viremia" (LOD<VL<1000 copies/mL on ART) 10605 "high viremia" (VL>1000 copies/mL on ART)	Higher incidence of hospitalization in elite than medical control, in particular for cardiovascular and psychiatric reasons	Age, female gen... IDU, low CD4 T... enrollment, HCV... HCV/HBV coinf...
Crowell et al, 2016 (30)	Retrospective cohort study – hospitalizations causes	33 "elite" (≥3 consecutive HIV-1 RNA measurements below LOD spanning ≥12 months) 188 "viremic" controllers (≥3 consecutive HIV-1 RNA measurements between LOD and 2000 copies/mL, spanning ≥12 months) 870 ART-controlled patients	No increase in the incidence of hospitalizations in controllers	Age and CD4 T... nadir
Stafford et al,	Retrospective cohort study - all	55 controllers (VL < 400 copies/mL during 2 years	19/55 developed complications after 11/8 years follow up.	HCV coinfectior...

2017 (31)	nADEs	without ART)	HCV/HIV co-infected controllers developed nADEs more rapidly than HIV mono-infected.	
Noel et al, 2019 (32)	Retrospective cohort study - focus on cardiovascular events	269 controllers (5 consecutive HIV VL < 400 copies/mL with at least 5 years FU without ART), including 61 patients with VL<50 copies/mL at enrollment	Very few cardiac or vascular event (n=10/269)	High blood pres

ART: antiretroviral therapy; FU: follow up; HBV: hepatitis B virus; HCV: hepatitis C virus; LOD: limit of detection; nADEs: non
defining events; VL: viral load

	Number of patients	Definition	Follow up	Response of CD4 T cell count	Other parameters	ART
Table 2. Overview of the main studies evaluating the outcome of ART-treated controllers.						
Okulicz et al. 2009 (22)	6 ECs 56 VirCs	ECs: ≥3 VLs below the DL for >12 months in the absence of ART VirCs: ≥3 VL below 2000 copies/mL for >12 months	48 months	EC: mean change +131/ µL at 24 months VirCs: mean change + 207/ µL at 24 months	Undetectable VL in 84% of ECs and 82% of VirCs at 24 months	*Ad libitum* (not provided)
Chun et al. (48) Kim et al. (49)	4 controllers (including 3 ECs)	Controllers and ECs are defined by the ability to suppress HIV plasma viremia to <500 and <50 copies of HIV RNA/mL, respectively, in the absence of ART with no more than 1 viral blip above these cut-off values	9 months	No change in the total CD4 T cell count (range at ART initiation: 560-980/ µL)	Undetectable VL in the sole controller with detectable VL at ART initiation (the other 3 remained undetectable) Reduction in the frequency of CD4 T cells carrying viruses No change in D-dimer or IL-6 levels, or the gut mucosal Th17 cell count	RAL TDF/FTC
Hatano et al. (50)	16 controllers, including 4 ECs with undetectable pre-ART VL	Plasma HIV RNA <1,000 copies/mL for 12 months	6 months	No impact	Decrease in plasma and rectal HIV RNA (mean decrease in the rectum: 0.61 log10) No significant decrease in	RAL TDF/FTC

					blood/rectal HIV DNA loads	
					Decrease in CD4 and CD8 T cell activation in blood and in CD8 activation in the rectum	
					No significant impact on usCRP, IL-6, sCD14, DDI	
Boufassa et al. (51)	34 controllers	ECs: ≥3 VLs below the detection level for >12 months in the absence of ART and 90% of the VLs <400 copies/ml with an infection known for more than 10 years	15 months	Blunted: + 80 CD4 T cells at 12 months	No	*Ad libitum*
Li et al. (52)	35 controllers (including 69% with pre-ART HIV RNA VL > 40 copies/mL)	≥2 VLs below 500 RNA copies/mL for >12 months in the absence of ART	24 months	No impact	Reduction in plasma HIV RNA levels measured by commercial assays and iSCA Reduction in the frequency of activated CD8 T cells and reduction in IP10 levels, but increased sCD163 levels	RPV TDF/FTC

ART: antiretroviral therapy; iSCA: integrase single-copy assay; EC: elite controller; HIC: HIV controller; VirC: viremic controller; VL: viral load; RAL: raltegravir; TDF/FTC: tenofovir-emtricitabine

Table 3. Proposals for the implementation (or not) of ART in controllers

Viremia	Other clinical parameters	Action
Clinically based propositions		
Detectable >1000 copies		Initiate ART
Consistently between 50 and 1000 copies	+ CD4+ T cell or CD4/CD8 ratio decline	Initiate ART
	Stable CD4+ T cell or CD4/CD8 ratio	Close follow-up
Intermittent blips	+ CD4+ T cell or CD4/CD8 ratio decline	Initiate ART
	Stable CD4+ T cell or CD4/CD8 ratio	Close follow-up
Situations to be discussed		
Undetectable	CD4+ T cell or CD4/CD8 ratio decline	Consider non-HIV-related comorbidities to be treated
Any viral load	Cardiovascular disease, obesity, smoking, HCV/HBV co-infection	Consider treatments of comorbidities
Any viral load	Cancer	Consider ART

Supplemental Table 1. A summary of international guidelines on the initiation of ART in controllers					
International AIDS Society (IAS) 2018 (Saag et al, JAMA. 2018 24;320(4):379–96.)	IAS guidelines, 2016 (Günthard et al, JAMA. 2016 Jul 12;316(2):191–210.)	Department of Health and Human Services (DDHS), October 2018	European AIDS Clinical Society (EACS) 9.0 October 2017	French ANRS expert group, May 2018	WHO guidelines on HIV/AIDS, June 2016
No specific new mention of controllers	Initiation of ART in "elite controllers" remains controversial (…). Initiation of treatment, however, is recommended for infected persons who have persistent undetectable viral load without ART but have declining CD4 cell counts.	There is a clear theoretical rationale for prescribing ART to HIV controllers even in the absence of detectable plasma HIV RNA levels. If ART is withheld, elite controllers should be followed closely, as some may experience CD4 cell decline, loss of viral control, or complications related to HIV infection.	ART should always be recommended irrespective of the CD4 count A possible exception could be persons with high CD4 counts and HIV-VL <1000 copies/mL	In the case of persons with stable CD4 T cell count >500/ µL and HIV-VL <1000 copies/mL, ART could be delayed	The ultimate decision to initiate ART rests with the PLWH. Motivation to start and adhere to treatment may be more difficult for people who feel well and have higher CD4 counts than for people who are or have been ill.