**SUPPLEMENTARY MATERIAL**

**Detailed METHODS section**

**Search strategies**

Records were retrieved from PubMed using the interface of the R-based tool Adjutant.1 The search strategy combined medical subject headings (MeSH terms) and other expressions commonly used to describe PLWH with impaired immune recovery despite virologic suppression during ART. The full expression used was:

(HIV[mh] OR HIV Infections[mh]) **AND** (*antiretroviral therapy, highly active[mh]* OR *ART* OR *antiretrovir\**)

**AND**

**(***((discordan\* OR impair\* OR incomplet\* OR insufficient\* OR low OR low-level OR poor OR suboptimal OR unfavorabl\* OR unsatisfactor\* OR weak) AND (immune OR immunologic\* OR CD4-Positive T-Lymphocytes[mh] OR CD4 Lymphocyte Count[mh] OR (CD4 AND (T-cell OR T-lymphocyt\*))) AND (gain\* OR reconstitut\* OR recover\* OR repopulat\* OR respon\* OR restorat\*))* **OR** *((immune OR immunologic\*) AND (discordan\*))***)**

**AND** "english"[Language] **AND** ("2009/01/01"[Date - Publication] : "2018/09/30"[Date - Publication])

Additional publications from Web of Science® were included after expert recommendation or scrutiny of reference lists.

**Eligibility criteria**

This review included all studies and reports meeting the following requirements:

1. Use of the concept of INR, with or without an explicit definition;
2. *Publication date*: between January 1, 2009, and September 30, 2018;
3. *Publication type*: original research articles; other types of articles were excluded (meeting abstracts, case reports, reviews and commentaries);
4. *Language*: written in English;
5. *Study population*: PLWH infected with HIV-1, on ART, over 15 year-old; in studies including participants with and without treatment only the group under ART was considered;
6. *Outcome measures*: “virologic suppression”, implicitly or explicitly defined as plasma HIV RNA copies below a threshold; “poor immune response to ART”, explicitly defined as not reaching a CD4 count, CD4+ T cell count change or slope, CD4/CD8 ratio or other immune recovery surrogate threshold.

All studies conducted on pregnant women or on individuals co-infected by HIV-2 were excluded.

**Screening procedure**

The list of publications obtained through Adjutant was exported to Microsoft Excel 2010 (Redmond, Washington, USA). This dataset had the following fields: PubMed Unique Identifier (PMID), year of publication, journal name, authors, title, abstract, article type, language, PMC citation count, PubMed Central identifier (pmcID), digital object identifier (DOI) and MeSH terms. A filter was applied to exclude records published before 2009 or not written in English. Publications retrieved from other sources were manually added to the dataset. Two researchers independently screened all titles and abstracts to assess whether the record should be included in the analysis, according to predefined criteria. All records with at least one favorable opinion transitioned to full-text screening.

Full-text pdf. files were obtained from the journal websites or by email request to the authors, and assessed using the reference manager Mendeley Desktop v1.19.1 (Mendeley, London, UK). Each full text was screened by one of two independent researchers to retrieve the following information: study characteristics (study type, recruitment period, number of total participants and INR participants enrolled), demographic characteristics of participants (age, sex assigned at birth, country), terminology (as explained in Data Analysis subsection) and criteria for INR definition [viral load threshold used to define virologic suppression, immune recovery surrogate, threshold and time point(s) used to assess immune response to ART]. The two researchers discussed dubious cases and/or consulted a third researcher until reaching consensus.

**Data analysis**

Country classification

Countries were categorized into low, lower-middle, upper-middle or high-income countries according to the Gross National Income per capita, as defined by the World Bank for 2017.2

Terminology

Many articles presented different terms to designate INR individuals. To analyse the diversity between publications, the term associated with the definition criteria stated in the methods section was selected as the most representative in each publication. When a unique term was not clear, the most prevalent term throughout the manuscript or the term used in the figures/tables or title was selected. Records were grouped by similar defining terms, and a table listing the distinct terms was produced.

INR criteria

In each study analysed, authors had defined one or more criteria to identify INR. These criteria included at least one immune recovery surrogate (CD4+ T cell count, its increase from baseline, its slope, CD4:CD8 ratio or other) and at least one threshold value for that surrogate. Criteria were considered as single when including only one surrogate and one threshold value, and as combined when including more than one surrogate or more than one threshold value, simultaneously or alternatively, independently of the assessment time point. Time points to assess INR status were expressed in time after ART initiation or time of virologic suppression. When the authors defined the time point as time “on suppressive ART”, it was considered that participants presented virologic suppression during that period. Authors expressed this period in weeks, months or years. To simplify comparison between studies, time points were first converted to months, as follows: 24 weeks equals 6 months; 36 weeks equals 9 months; 48 and 52 weeks equal 12 months; and 96 weeks equals 24 months. Records were then grouped by similar criteria, and two tables listing single and combined criteria were produced.

Independent publications

To complement the analysis of terminology and criteria diversities, the number of publications with no authors in common (ni) was assessed for each term and each criterion found. In publications based on large national or international collaborations, *i.e.* with more than 20 authors listed, only the named authors were considered for this analysis.

**Figure S1** - Number of publications per year and cumulative sum (2009-2018).

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**Figure S2** - Percentage of male participants (sex assigned at birth) in each study, by country classification, according to 2017 income. HIC, high-income countries; LIC, low-income countries; LMIC, lower-middle-income countries; UMIC, upper-middle-income countries.

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**TABLE S1** - Data on the 103 publications included in the systematic review.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *1* | Lee SC, *Sci Rep*, 2018 | Malaysia | Cross-sectional | 100 % | Suboptimal immune recovery (sIR) | CD4 count < 350 cells/µL  after ≥ 24 mos. of VS | < 50 copies/mL  for ≥ 24 mos. | [119] |
| *2* | De Benedetto I, *JAIDS*, 2018 | Italy | Cross-sectional | 79 % | Immunological non responders (INRs) | CD4 count ≤ 350 cells/µL  after ≥ 24 mos. of ART | < 50 copies/mL  for ≥ 12 mos. | [63] |
| *3* | Rosado-Sánchez I, *Front Immunol*, 2018 | Ivory Coast | Longitudinal | NA | Low CD4-recovery subjects (LR-subjects) | CD4 count < 250 cells/µL  after ≥ 24 mos. of VS | NA | [95] |
| *4* | Lu W, *Front Microbiol*, 2018 | Italy | Cross-sectional | 100 % | Immunological non-responders (INRs) | CD4 count < 350 cells/µL  after ≥ 24 mos. of ART | Below the detection limit for ≥ 24 mos. | [25] |
| *5* | Tasca KI, *J Immunol Res*, 2018 | Spain | Cross-sectional | 60 % | Inadequate CD4+ T cell recovery (tIR) | CD4 count < 500 cells/µL  after ≥ 60 mos. of ART | ≤ 50 copies/mL  after 60 mos. of ART | [84] |
| *6* | Logerot S, *AIDS*, 2018 | Germany | Experimental | 72 % | Poor immunological responder (PIR) | CD4 count < 350 (101-350)  after ≥ 24 mos. of ART[[1]](#footnote-1) | < 50 copies/mL  for ≥ 18 mos. | [106] |
| *7* | Bandera A, *Front Immunol*, 2018 | Italy | Cross-sectional | 85 % | Immunological non-responders (INR) | CD4 count ≤ 350 cells/µL  ≥ 24 mos. of ART | < 50 copies/mL  for ≥ 12 mos. | [61] |
| *8* | Wójcik-Cichy K, *Arch Immunol Ther Exp*, 2018 | Poland | Cross-sectional | 74 % | Suboptimal CD4 recovery | CD4 count < 350 cells/µL  after ≥ 24 mos. of ART | < 50 copies/mL  for ≥ 12 mo | [112] |
| *9* | Mupfumi L, *PLoS One*, 2018 | Botswana | Longitudinal | 32 % | Immunologic non-response | CD4 change < 20 %  within 6 mos. of ART | < 400 copies/mL  after 6 mos. of ART | [74] |
| *10* | Rodríguez-Gallego E, *AIDS*, 2018 | Spain | Longitudinal | 78 % | Immunological non-responders (INR) | CD4 count < 250 cells/µL  at 36 mos. of ART | NA | [75] |
| *11* | Darraj M, *J Infect Public Health*, 2017 | Italy | Longitudinal | 74 % | Immune reconstitution failure | CD4 count < 200 cells/µL OR  CD4 change < 100 cells/µL  up to 12 mos. of VS | < 50 copies/mL (time point or period NA) | [58] |
| *12* | Gomez-Mora E, *PLoS One*, 2017 | Spain | Cross-sectional | 77 % | Immunodiscordant | CD4 count < 350 cells/µL  on long term ART (median 127 mos.) | < 50 copies/mL (time point or period NA) | [43] |
| *13* | Giuliani E, *Immunol Lett*, 2017 | Italy | Cross-sectional | 75 % | Poor CD4+ T-cell recovery | CD4 count < 350 cells/µL  at 24 to 49 (IQR) mos. of ART | Below the detection limit. ART for ≥ 24 mos. | [100] |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *14* | Gunda DW*, BMC Res Notes*, 2017 | Tanzania | Longitudinal | 33 % | Poor immune recovery | CD4 count < 350 cells/µL  at 48 mos. of follow-up (ART) | NA | [107] |
| *15* | Rosado-Sanchez I, *Antimicrob Agents Chemother*, 2017 | Spain | Longitudinal | 89 % | Low CD4-recovery subjects (LR subjects) | CD4 count < 250 cells/µL  after ≥ 24 mos. of VS; CD4 count at baseline < 200 cells/µL | NA | [96] |
| *16* | Rosado-Sanchez I, *Antiviral Res*, 2017 | Spain | Longitudinal | 100 % | Low CD4-recovery subjects (LR subjects) | CD4 count < 250 cells/µL  after ≥ 24 mos. of VS; CD4 count at baseline < 200 cells/µL | NA | [97] |
| *17* | Minami R, *J Infect Chemother*, 2017 | Japan | Experimental | 100 % | Immunological non-responder | CD4 count < 350 cells/µL  at 27.5 ± 5.3 (mean ± SEM) mos. of ART | Below the detection limit for ≥ 6 mos. | [73] |
| *18* | Raffi F, *J Antimicrob Chemother*, 2017 | France | Longitudinal | 80 % | Failure to achieve CD4 response/  Failure to achieve complete immunological response | More than one CD4 count < 500 cells/µL in the last 18 months, after 120 mos. of ART / (More than one CD4 count < 500 cells/µL OR more than one CD4:CD8 ratio < 1 in the last 18 months, after 120 mos. of ART) | < 50 copies/mL for ≥ 12 mos. with no more than 1 viral blip (50-500 copies/mL) | [57] |
| *19* | Stiksrud B, *JAIDS*, 2016 | Norway | Cross-sectional | 79 % | Immunological non-responder (INR) | CD4 count < 400 cells/µL  after ≥ 24 mos. of ART | ≤ 20 copies/mL for ≥ 18 mos. | [80] |
| *20* | Kayigamba FR, *PLoS One*, 2016 | Rwanda | Longitudinal | 38 % | Immunological cART discordance | CD4 change < 100 cells/µL  at 12 mos. compared to baseline | < 40 copies/mL at 12 mos. | [44] |
| *21* | Perez-Santiago J, *AIDS*, 2016 | Spain | Cross-sectional | 76 % | Immunodiscordant subgroups | CD4+ T-cell count < different cutoff values ranging from 200 to 600 cells/µl OR CD4+ T-cell count change < different values ranging from 50 to 500 cells/µl after ≥ 24 mos. of VS | < 50 copies/mL for ≥ 24 mos. | [51] |
| *22* | Girard A, *JAIDS*, 2016 | France | Cross-sectional | 86 % | Immunological non-responder (INRs) | CD4 count < 500 cells/µL  after ≥ 36 mos. of VS | < 40 copies/mL for ≥ 36 mos. | [66] |
| *23* | Menkova-Garnier I, *PLoS* Pathog, 2016 | France | Cross-sectional | 34 % | Immunological non-responders (INRs) | CD4 count < 500 cells/µL  AND CD4:CD8 ratio < 1  after ≥ 96 mos. of VS | Below the detection limit for ≥ 96 mos. | [32] |
| *24* | El-Beeli M, *Hum Immunol*, 2016 | Oman | Longitudinal | 45 % | Poor immune responder | CD4 change < 50 cells/µL  per year | < 50 copies/mL at ≥ 12 mos. | [108] |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *25* | Tincati C, *AIDS*, 2016 | Italy | Cross-sectional | 90 % | Immunological nonresponders (INR) | CD4 count < 350 cells/µL  AND/OR CD4 change < 30 %  after ≥ 12 mos. of ART | < 40 copies/mL at ≥ 12 mos. | [81] |
| *26* | Nakanjako D, *AIDS*, 2016 | International | Longitudinal | NA | Sub-optimal immune responders (SO-IR) | CD4+ T-cell count < different cutoff values (200, 350 or 500 cells/µl) up to 60 mos. of ART | NA | [120] |
| *27* | Thiebaut R*, Clin Infect Dis*, 2016 | International | Experimental | 70 % | Low CD4 T-cell reconstitution | CD4 count < 400 (101-400) cells/µL  after ≥ 12 mos. of ART | < 50 copies/mL at ≥ 12 mos. | [13] |
| *28* | Valiathan R, *Immunobiology*, 2016 | USA | Cross-sectional | 70 % | (Immunologically) discordant patients | CD4 count < 200 cells/µL OR (CD4:CD8 ratio < 1 AND CD4 count < 400 cells/µL AND CD4 change < 100 cells/µL)  after ≥ 24 mos. of VS | < 50 copies/mL for ≥ 24 mos. | [34] |
| *29* | Shive CL, *JAIDS*, 2016 | USA | Cross-sectional | NA | Immune failure patients | CD4 count < 350 cells/µL  after ≥ 24 mos. of ART | < 50 copies/mL at ≥ 24 mos. | [59] |
| *30* | Shmagel NG, ﻿*Dokl Biochem Biophys*, 2015 | Russia | Cross-sectional | 62 % | Discordant response of CD4+ T cells | CD4 count < 350 cells/µL  after ≥ 24 mos. of ART | < 50 copies/mL at ≥ 24 mos. | [39] |
| *31* | Zhang F, ﻿ *Biosci Trends*, 2015 | China | Longitudinal | NA | Suboptimal CD4+ T-cell recovery | CD4 count < 350 cells/µL  at 12 mos. of ART | NA | [113] |
| *32* | Cillo AR, *AIDS*, 2015 | USA | Experimental | 94 % | Suboptimal CD4+ T-cell recovery | CD4 count < 250 cells/µL after 22 to 54 (IQR) mos. of ART AND slope of annual change [-20; +20] cells/µL in the last 12 mos. | < 50 copies/mL | [16] |
| *33* | Kye-Hyung K, *Korean J Intern Med*, 2015 | South Korea | Longitudinal | 85 % | Immunologic non-responder | CD4 count < 500 cells/µL  after ≥ 48 mos. of VS | < 50 copies/mL for ≥ 48 mos. | [68] |
| *34* | van Lelyveld SFL, *PLoS One*, 2015 | Netherlands | Experimental | 94 % | Suboptimal immunological response | CD4+ T-cell count < 200 cells/µL after ≥ 12 mos. of ART OR CD4+ T-cell count  < 350 cells/µL after ≥ 24 mos. of ART | < 50 copies/mL for ≥ 6 mos. | [14] |
| *35* | Massanella M, *J Transl Med*, 2015 | Spain | Cross-sectional | 88 % | (Immuno)discordant patients | CD4 count < 350 cells/µL  after ≥ 24 mos. of ART | < 50 copies/mL for ≥ 24 mos. | [46] |
| *36* | Batista G, *Med Mal Infect*, 2015 | Senegal | Longitudinal | 35 % | Suboptimal immune reconstitution (SIR) | CD4 change < 50 cells/µL  up to 6 mos. of ART | < 50 copies/mL up to 6 mos. | [121] |
|  |  |  |  |  |  |  |  |  |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *37* | Li T, *HIV Clin Trials*, 2015 | China | Experimental | 89 % | Immune non-responders | CD4 count < 200 cells/µL OR CD4 count < 20 % increase compared to baseline after ≥ 12 mos. | < 40 copies/mL at ≥ 24 mos. | [69] |
| *38* | Pacheco YM, *Antiviral Res*, 2015 | Spain | Longitudinal | 78 % | Low CD4-group | CD4 count < 250 cells/µL  at 24 mos. of ART | < 500 copies/mL for ≥ 24 mos. | [31] |
| *39* | Mingbunjerdsuk P, *Jpn J Infect Dis*, 2015 | Thailand | Longitudinal | 68 % | Immunological discordance | CD4 count < 200 cells/µL at 12 mos. of VS OR CD4 change < 30 % at 12 mos. compared to baseline | < 50 copies/mL up to 12 mos. | [49] |
| *40* | Nakanjako D, *Trop Med Int Health*, 2015 | Uganda | Experimental | NA | Suboptimal immune responders (SO-IR) | CD4 change < 25th percentile (295 cells/µL) at 84 mos. of ART compared to baseline | < 400 copies/mL from 6 mos. of ART | [15] |
| *41* | Somsouk M, *PLoS One*, 2014 | USA | Experimental | 100 % | Incomplete CD4+ T cell recovery | CD4 count < 350 cells/µL after ≥ 12 mos. of VS AND CD4 change < 100 cells/µL in the last year | < 40 copies/mL for ≥ 12 mos. | [17] |
| *42* | Saidakova EV, ﻿ *Dokl Biol Sci*, 2014 | Russia | Cross-sectional | NA | Immunological nonresponders (IN) | CD4 count < 350 cells/µL  after 24 mos. of ART | < 50 copies/mL at 24 mos. of ART | [77] |
| *43* | Asmelash A, *BMC Infect Dis*, 2014 | International | Longitudinal | 0 % | Suboptimal CD4 response (SCR) | CD4 count < 350 cells/µL AND CD4 change < 100 cells/µL at 12 mos. of ART compared to baseline | < 400 copies/mL for 12 mos. | [114] |
| *44* | Routy JP, *HIV Med*, 2014 | Canada | Experimental | 95 % | Immune nonresponding HIV-infected patients | CD4 count < 350 cells/µL  after ≥ 9 mos. of VS | < 50 copies/mL for ≥ 9 mos. | [76] |
| *45* | Jacobson JM, *JAIDS*, 2014 | USA | Experimental | 91 % | Poor CD4 lymphocyte recovery | CD4 count < 200 cells/µL  after ≥ 6 mos. of VS | ≤ 200 copies/mL for ≥ 6 mos. | [26] |
| *46* | Gaardbo JC, *JAIDS*, 2014 | Denmark | Longitudinal | 86 % | Immunological nonresponders (INR) | CD4 count < 200 cells/µL  after ≥ 24 mos. of VS | ≤ 200 copies/mL for ≥ 24 mos. | [65] |
| *47* | Takuva S, *J Int AIDS Soc*, 2014 | South Africa | Longitudinal | 36 % | Poor CD4 recovery | CD4 count < 200 cells/µL OR CD4 change < different cutoffs ( < 0, 0-49, or 50-99 cells/µL) at 6 mos. of ART compared to baseline | < 400 copies/mL at 6 mos. of ART | [101] |
| *48* | Zoufaly A, *PLoS One*, 2014 | International | Longitudinal | 72 % | Immuno-virological discordance (ID) | CD4 count < pre-ART value  at 0-6, 7-12, 13-18, 19-24 and >24 mos. of VS | ≤ 50 copies/mL | [54] |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *49* | Bayigga L, *BMC Immunol*, 2014 | Uganda | Longitudinal | NA | Suboptimal immune responders | CD4 change < 25th percentile (199 cells/µL) after 48 mos. of ART compared to baseline | < 400 copies/mL for ≥ 6 mos. | [122] |
| *50* | Saison J, *Clin Exp Immunol*, 2014 | France | Cross-sectional | 71 % | Inadequate immunological responder group (iIR group) | CD4 count < 500 cells/µL  after ≥ 12 mos. of VS | < 50 copies/mL at ≥ 12 mos. | [33] |
| *51* | Engsig FN, *Clin Infect Dis*, 2014 | International | Longitudinal | NA | Incomplete CD4 recovery | CD4 count ≤ 200 cells/µL  after ≥ 36 mos. of VS | ≤ 500 copies/mL for ≥ 36 mos. | [85] |
| *52* | Asdamongkol N, *Jpn J Infect Dis,* 2013 | Thailand | Experimental | 68 % | Immunological discordance | CD4 count < 200 cells/µL AND CD4 count increase < 30 % at 12 mos. of VS compared to baseline | < 40 copies/mL for ≥ 12 mos. | [40] |
| *53* | Rusconi S, *PLoS One*, 2013 | Italy | Experimental | 82 % | Immunological non-responders (INRs) | CD4 count ≤ 200 cells/µL AND/OR CD4 count increase < 25 % after ≥ 12 mos. of ART compared to baseline | < 50 copies/mL for ≥ 12 mo | [18] |
| *54* | Sennepin A, *AIDS*, 2013 | France | Longitudinal | 75 % | Immunological nonresponders (InRs) | CD4 count < 350 cells/µL  for ≥ 24 mos. of ART | < 40 copies/mL for ≥ 24 mos. | [78] |
| *55* | Su QJ, *Int J STD AIDS*, 2013 | China | Experimental | 56 % | Insufficient CD4+ T-cell response | CD4 count increase < 100 cells/µL  after 12 mos. of ART | < 50 copies/mL for ≥ 12 mos. | [89] |
| *56* | Rallon N, *J Antimicrob Chemother*, 2013 | Spain | Cross-sectional | 82 % | Poor immunological response | CD4 change < 200 cells/µL  after long-term ART | < 50 copies/mL | [109] |
| *57* | Nakanjako D, *BMC Immunol*, 2013 | Uganda | Longitudinal | 43 % | Suboptimal immune responders | CD4 count increase < 25th percentile (298 cells/µL) after 48 mos. of ART compared to baseline | NA | [124] |
| *58* | Negredo E, *J Antimicrob Chemother*, 2013 | Spain | Experimental | 86 % | Immunodiscordant response | CD4 count < 350 cells/µL  after ≥ 24 mos. of VS | NA | [56] |
| *59* | Hunt PW, *Blood*, 2013 | USA | Experimental | 96 % | Incomplete CD4+ T cell recovery | CD4 count < 350 cells/µL  for ≥ 12 mos. | NA | [87] |
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|  |  |  |  |  |  |  |  |  |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *60* | Anude CJ, *BMC Infect Dis*, 2013 | Nigeria | Longitudinal | 36 % | Immunologic failure with virologic success (VL+/CD4-) | CD4 count ≤ pre-ART value OR CD4 change < 50 cells/µL at 12 mos. of ART compared to baseline | < 400 copies/mL at 12 mos. of ART | [60] |
| *61* | Horta A, *PLoS One*, 2013 | Portugal | Cross-sectional | 79 % | Immunological non responders | CD4 count < 500 cells/µL  after ≥ 60 mos. of ART | ≤ 50 copies/mL for ≥ 12 mos. | [67] |
| *62* | Helleberg M, *AIDS*, 2013 | Denmark | Cross-sectional | NA | Poor CD4 response | CD4 change < 25 or [25; 100] cells/µL after 24 mos. of ART | < 400 copies/mL ≥ 12 mos. of ART | [105] |
| *63* | Massanella M, *AIDS*, 2012 | Spain | Experimental | 86 % | Immunodiscordant patients | CD4 count < 350 cells/µL  after > 24 mos. of VS | < 50 copies/mL for > 24 mos. | [48] |
| *64* | Cuzin L, *JAIDS*, 2012 | France | Experimental | 92 % | Insufficient immunological restoration | All CD4 counts < 350 cells/µL  AND regression slope < 50 cells/µL/year during the last 24 mos. | < 50 copies/mL for 24 mos. | [90] |
| *65* | Lichtenstein KA, *Antivir Ther,* 2012 | USA | Experimental | 97 % | Poor CD4+ T-cell responses | CD4 count < 350 cells/µLfor ≥ 12 mos. of ART OR CD4 change persistently < 0 for ≥ 24 mos. | Median < 48 copies/mL at ≥ 12 mos. of ART | [102] |
| *66* | Wilkin TJ, *J Infect Dis*, 2012 | USA | Experimental | 94 % | Suboptimal CD4+ T-cell recovery | CD4 count < 250 cells/µL  AND slope between [-20; +20] cells/µL/year during the last 12 mos. | Below the detection limit for ≥ 12 mos. | [20] |
| *67* | Mendez-Lagares G, *J Infect Dis*, 2012 | Spain | Cross-sectional | 74 % | Low-level CD4 T cell repopulation group (LLR patients) | CD4 count < 250 cells/µL  after ≥ 24 mos. of VS | < 50 copies/mL for ≥ 24 mos. | [91] |
| *68* | Julg B, *PLoS One*, 2012 | South Africa | Longitudinal | 39 % | Discordant virological and immunological responses | CD4 count < 200 cells/µL  at 12 mos. of ART OR CD4 count < 500 cells/µL at 30 mos. of ART | < 50 copies/mL within the first 12 mos. | [55] |
| *69* | Mendez-Lagares G, *J Antimicrob Chemother*, 2012 | Spain | Cross-sectional | 80 % | Low-level CD4 T cell repopulation (LLR patients) | CD4 count < 250 cells/µL  after ≥ 24 mos. of VS | < 50 copies/mL for ≥ 24 mos. | [92] |
| *70* | van Lelyveld SFL, *AIDS*, 2012 | Netherlands | Longitudinal | 83 % | Poor immunological recovery | CD4 count < 200 cells/µL  after 24 mos. of ART | < 500 copies/mL within 9 mos. and after 18-24 mos. of ART | [110] |
|  |  |  |  |  |  |  |  |  |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *71* | Casotti JAS, *Rev Inst Med Trop Sao Paulo*, 2011 | Brazil | Cross-sectional | NA | Discordant immunologic and virologic responses | CD4 counts persistently < 350 cells/µL over the last 6 mos (≥ 12 mos. of ART and ≥ 6 mos. of VS) | < 50 copies/mL for ≥ 6 mos. | [41] |
| *72* | Soria A, *PLoS One*, 2011 | Italy | Cross-sectional | 73 % | Immunological non responders (INR) | CD4 count < 200 cells/µL  after > 12 mos. of ART | < 50 copies/mL over the last 6 mos. | [79] |
| *73* | Casotti JAS, *BMC Infect Dis*, 2011 | Brazil | Cross-sectional | 78 % | Paradoxical immunological response (PIR) | CD4 count < 350 cells/µL  after ≥ 12 mos. of VS | < 50 copies/mL for ≥ 12 mos. | [99] |
| *74* | Fernandez S, *J Infect Dis*, 2011 | Australia | Cross-sectional | 95 % | CD4+ T-cell deficiency | CD4 count < median (490 cells/µL)  after > 12 mos. of ART and ≥ 6 mos. of VS | < 50 copies/mL for ≥ 6 mos. | [38] |
| *75* | Byakwaga H, *J Infect Dis*, 2011 | Australia | Experimental | 92 % | Suboptimal CD4+ T-cell response | CD4 count < 350 cells/µL in the last 6 mos. AND CD4 change < 50 cells/µL in the last 12 mos. | < 50 copies/mL in the last 9 mos. | [115] |
| *76* | Choi JY, *JAIDS*, 2011 | International | Longitudinal | 84 % | Virologic-only response (VR+IR-) | (CD4 count <350 cells/µL OR change < 50 cells/µL at 6 mos. of ART) OR (CD4 count < 350 cells/µL OR CD4 change < 100 cells/µL at 12 or 24 mos. of ART) | < 500 copies/mL at 6, 12 and 24 mos. of ART | [125] |
| *77* | Tanaskovic S, *AIDS*, 2011 | Australia | Longitudinal | 100 % | Poor recovery of CD4+ T cells | CD4 count < 500 cells/µL  at > 12 mos. of ART | < 50 copies/mL for ≥ 6 mos. | [103] |
| *78* | Hunt PW, *J Infect Dis*, 2011 | USA | Experimental | 93 % | Incomplete CD4+ T cell recovery | CD4 count < 350 cells/µL  for ≥ 12 mos. (after ≥ 6 mos. of ART) | Most participants  with < 75 copies/mL | [86] |
| *79* | Merlini E, *PLoS One*, 2011 | Italy | Longitudinal | 77 % | Immunological non responders (INRs) | CD4 count < 200 cells/µL  at 12 mos. of ART | < 60 copies/mL for ≥ 12 mos. | [72] |
| *80* | Hatano H, *J Infect Dis*, 2011 | USA | Experimental | 97 % | Suboptimal CD4+ T cell response | CD4 count < 350 cells/µL  for ≥ 12 mos. of VS | < 75 copies/mL for ≥ 12 mos. | [116] |
| *81* | Nakanjako D, *BMC Infect Dis*, 2011 | Uganda | Longitudinal | 25 % | Suboptimal CD4 reconstitution | CD4 change < 25th percentile (199 cells/µL) at 48 mos. of ART compared to baseline | < 400 copies/mL for 48 mos. | [117] |
| *82* | Zoufaly A, *J Infect Dis*, 2011 | Germany | Longitudinal | 77 % | Immuno-virological discordance | CD4 count < 200 cells/µL  at 0-6, 7-12, 13-24 or > 24 mos. of VS | < 50 copies/mL for 0-6, 7-12, 13-24 or > 24 mos. | [53] |
|  |  |  |  |  |  |  |  |  |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *83* | Grabmeier-Pfistershammer K, *JAIDS*, 2011 | Austria | Cross-sectional | NA | Nonimmune reconstituters (non-IR) | CD4 count < 300 cells/µL OR CD4 change < 250 cells/µL  for ≥ 12 mos. of VS | Below the detection limit (NA) | [98] |
| *84* | Bellistri GM, PLoS One, 2010 | Italy | Cross-sectional | 87 % | Immunological nonresponders (INRs) | CD4 count ≤ 200 cells/µL  after ≥ 6 mos. of ART  (mean ART length of 29 months) | ≤ 50 copies/mL (time point or period NA) | [62] |
| *85* | Loutfy MR, *JAIDS*, 2010 | Canada | Longitudinal | 83 % | immunologic discordance | CD4 count < 200 cells/µL  at 12 and 24 mos. of ART | < 50 copies/mL at 12 [9; 15] mos. of ART | [45] |
| *86* | Engsig FN, *BMC Infect Dis*, 2010 | Denmark | Longitudinal | 78 % | Immunological non-responders (INRs) | CD4 count ≤ 200 cells/µL  after 36 mos. of VS | < 50 (199 or 399) copies/mL for ≥ 36 mos. | [64] |
| *87* | Marchetti G, *AIDS*, 2010 | Italy | Cross-sectional | 81 % | Immunological nonresponders (INRs) | CD4 count ≤ 200 cells/µL  after ≥ 24 mos. of ART; CD4 nadir < 100 cells/µL | < 50 copies/mL over the last 6 months | [71] |
| *88* | Hermans SM, *PLoS One*, 2010 | Uganda | Longitudinal | 34 % | Suboptimal immune response | CD4 count < 200 cells/µL  OR CD4 change < 200 cells/µL  at 24 mos. of ART | < 400 copies/mL during the first 6-12 mos. of ART | [123] |
| *89* | Negredo E, *Clin Infect Dis*, 2010 | Spain | Cross-sectional | 77 % | Discordant patients | CD4 count always < 350 cells/µL  for > 24 mos. | < 50 copies/mL for > 24 mos. | [50] |
| *90* | Massanella M, *AIDS*, 2010 | Spain | Cross-sectional | 77 % | Discordant patients | CD4 count < 350 cells/µL  after > 24 mos. of VS | < 50 copies/mL for ≥ 24 mos. | [47] |
| *91* | Sachdeva N, *Viral Immunol*, 2010 | USA | Longitudinal | 78 % | Discordant patients | CD4 count < 200 cells/µL OR (CD4 count < 400 cells/µL, CD4 change ≤ 100 cells/µL and CD4:CD8 ratio < 1) after ≥ 12 mos. of VS | < 50 copies/mL for ≥ 12 mos. | [52] |
| *92* | Erikstrup C, *JAIDS*, 2010 | Denmark | Longitudinal | 94 % | Impaired CD4 cell recovery | CD4 count < 200 cells/µL  after 36 mos. of VS | < 50 copies/mL for ≥ 36 mos. | [82] |
| *93* | Tuboi SH, *JAIDS*, 2010 | International | Longitudinal | 39 % | Virologic only response (VR+IR-) | CD4 change < 50 cells/µL at 6 [3; 9] mos. of ART compared to baseline | < 500 copies/mL at 6 mos. of ART | [126] |
| *94* | Woelk CH, *AIDS*, 2010 | USA | Longitudinal | 100 % | Poor CD4+ T-cell recovery group | CD4 change < 200 cells/µL  at 12 mos. of ART | < 50 copies/mL during 12 mos. | [104] |
|  |  |  |  |  |  |  |  |  |
| No. | First author, *Journal*,  Year of publication | Country / International | Study type | Male percentage among total participants | Representative INR term | INR criteria  (immune recovery surrogate,  threshold and time point or period) | Viral load (threshold and time point or period) | Ref. (main text) |
| *95* | Gilson RJC, *HIV Med*, 2010 | UK | Longitudinal | 75 % | Discordant responders | CD4 change < 100 cells/µL  at 6 [6; 10] or 12 [10;14] mos. of ART compared to baseline | < 50 copies/mL within 6 mos. of ART | [42] |
| *96* | Magen E, *Int J Infect Dis*, 2010 | Israel | Experimental | 61 % | Immunological non-responders | CD4 count < 300 cells/µL AND CD4 change < 10% after ≥ 12 mos. of ART compared to baseline | < 400 copies/mL for > 12 mos. | [70] |
| *97* | Pacheco YM, *Curr HIV Res*, 2009 | Spain | Longitudinal | 75 % | low-level CD4 counts repopulation group (Low-group) | CD4 count < 250 cells/µL  at 24 mos. of ART | < 1000 copies/mL during the first 24 mos. of ART | [94] |
| *98* | Mavigner M, *PLoS One*, 2009 | France | Cross-sectional | 87 % | Poor immunological responders | CD4 change < 200 cells/µL  after 60 to 94 (IQR) mos. of ART | < 50 copies/mL  for 84 mos. (median) | [111] |
| *99* | Molina-Pinelo S, *J Antimicrob Chemother*, 2009 | Spain | Cross-sectional | 86 % | Low-level CD4 T cell repopulation patients | CD4 count ≤ 250 cells/µL  after ≥ 12 mos. of ART | < 50 copies/mL for ≥ 12 mos. | [93] |
| *100* | Stepanyuk O, *AIDS*, 2009 | USA | Longitudinal | 100 % | Impaired CD4 recovery | CD4 count < 250 cells/µL  ≥ 12 mos. of VS | < 50 copies/mL for ≥ 12 mos. | [83] |
| *101* | Önen NF, *HIV Med*, 2009 | USA | Longitudinal | 75 % | Sub-optimal CD4 recovery | CD4 change < 150 cells/µL  until 12 mos. of ART compared to baseline | < 400 (before 1999) or < 50 (thereafter) copies/mL at 12 mos. | [118] |
| *102* | van Griensven J, *JAIDS*, 2009 | Rwanda | Longitudinal | 27 % | Virologic-only response (VR+IR-) | CD4 change < 50 cells/µL  at 12 mos. of ART compared to baseline | < 40 copies/mL at 12 mos. of ART | [127] |
| *103* | Falster K, *JAIDS*, 2009 | Australia | Longitudinal | 94 % | Incomplete immune response | CD4 counts < 350 cells/µL  in the 12–24 months after starting the first or second cART regimen | < 400 copies/mL at ≥ 9 mos. | [88] |

**Note:** Publications are ordered by year of publication.

ART, antiretroviral therapy; cART, combination antiretroviral therapy; CD4 count, CD4+ T cell count; CD4 change, CD4+ T cell count change; INR, immunological non-response; IQR, interquartile range; NA, not available; Ref., reference; SEM, standard error of mean; UK, United Kingdom; USA, United States of America; VS, virologic suppression.

**TABLE S2** - List of scientific journals in which the included records were published, and number of publications per journal.

|  |  |  |
| --- | --- | --- |
|  | Journal title (*NLM Abbreviation*) | No. of publications |
| *1* | Antimicrobial agents and chemotherapy (*Antimicrob Agents Chemother*) | 1 |
| *2* | Antiviral therapy (*Antivir Ther*) | 1 |
| *3* | Archivum immunologiae et therapiae experimentalis (*Arch Immunol Ther Exp*) | 1 |
| *4* | Bioscience trends (*Biosci Trends*) | 1 |
| *5* | Blood (*Blood*) | 1 |
| *6* | BMC research notes (*BMC Res Notes*) | 1 |
| *7* | Clinical and experimental immunology (*Clin Exp Immunol*) | 1 |
| *8* | Current HIV research (*Curr HIV Res*) | 1 |
| *9* | Doklady biological sciences (*Dokl Biol Sci*) | 1 |
| *10* | Doklady. Biochemistry and biophysics (*Dokl Biochem Biophys*) | 1 |
| *11* | Frontiers in microbiology (*Front Microbiol*) | 1 |
| *12* | HIV clinical trials (HIV Clin Trials) | 1 |
| *13* | Human immunology (*Hum Immunol*) | 1 |
| *14* | Immunobiology (*Immunobiology*) | 1 |
| *15* | Immunology letters (*Immunol Lett*) | 1 |
| *16* | International journal of infectious diseases (*Int J Infect Dis*) | 1 |
| *17* | International journal of STD & AIDS (*Int J STD AIDS*) | 1 |
| *18* | Journal of immunology research (*J Immunol Res*) | 1 |
| *19* | Journal of infection and chemotherapy (*J Infect Chemother*) | 1 |
| *20* | Journal of infection and public health (*J Infect Public Health*) | 1 |
| *21* | Journal of the International AIDS Society (*J Int AIDS Soc*) | 1 |
| *22* | Journal of translational medicine (*J Transl Med*) | 1 |
| *23* | Medecine et maladies infectieuses (*Med Mal Infect*) | 1 |
| *24* | PLoS pathogens (*PLoS Pathog*) | 1 |
| *25* | Revista do Instituto de Medicina Tropical de Sao Paulo (*Rev Inst Med Trop Sao Paulo*) | 1 |
| *26* | Scientific reports (*Sci Rep*) | 1 |
| *27* | The Korean journal of internal medicine (*Korean J Intern Med*) | 1 |
| *28* | Tropical medicine & international health (*Trop Med Int Health*) | 1 |
| *29* | Viral immunology (*Viral Immunol*) | 1 |
| *30* | Antiviral research (*Antiviral Res*) | 2 |
| *31* | BMC immunology (*BMC Immunol*) | 2 |
| *32* | Frontiers in immunology (*Front Immunol*) | 2 |
| *33* | Japanese journal of infectious diseases (*Jpn J Infect Dis*) | 2 |
| *34* | Clinical infectious diseases (*Clin Infect Dis*) | 3 |
| *35* | HIV medicine (*HIV Med*) | 3 |
| *36* | BMC infectious diseases (*BMC Infect Dis*) | 5 |
| *37* | The Journal of antimicrobial chemotherapy (*J Antimicrob Chemother*) | 5 |
| *38* | The Journal of infectious diseases (*J Infect Dis*) | 7 |
| *39* | Journal of acquired immune deficiency syndromes (*J Acquir Immune Defic Syndr, JAIDS*) | 14 |
| *40* | PloS one (PLoS One) | 14 |
| *41* | AIDS - London, England (*AIDS*) | 15 |

**TABLE S3** - Countries involved in the large international collaborations/consortia.

|  |  |
| --- | --- |
| International project | Countries/Region |
| Antiretroviral Therapy Cohort Collaboration (ART-CC) | Austria, Canada, Denmark, France, Germany, Italy, Netherlands, Spain, Switzerland, United Kingdom, United States of America |
| Antiretroviral Therapy in Lower Income Countries Collaboration (ART-LINC) | Africa (Botswana, Burundi, Cameroon, Democratic Republic of Congo, Côte d’Ivoire, Kenya, Malawi, Morocco, Nigeria, Rwanda, Senegal, South Africa, and Uganda), Brazil, India, Thailand |
| Collaboration of Observational HIV Epidemiological Research Europe (COHERE) | Argentina, Austria, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Georgia, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom |
| EuroSIDA Study Group | Argentina, Austria, Belarus, Belgium, Bosnia-Herzegovina, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Georgia, Greece, Hungary, Iceland, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom |
| TREAT Asia HIV Observational Database (TAHOD) | Australia, China, India, Malaysia, Philippines, Singapore, Taiwan, Thailand, United States of America |

**TABLE S4** – Enrolment countries and its classification by income in 2017.

|  |  |
| --- | --- |
| Countries  (n = 30) | Country classification by income  (Gross National Income per capita in 2017) |
| Rwanda  Senegal  Tanzania  Uganda | Low-income country ($995 or less) |
| Nigeria | Lower-middle-income ($996 to $3895) |
| Botswana  Brazil  China  Malaysia  Russia  South Africa  Thailand | Upper-middle-income ($3896 to $12055) |
| Australia  Austria  Canada  Denmark  France  Germany  Israel  Italy  Japan  Netherlands  Norway  Oman  Poland  Portugal  South Korea  Spain  United Kingdom  United States of America | High-income ($12056 or more) |

**Reference:** The World Bank. How we classify countries. Available at: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed on November 23, 2018.

**TABLE S5** - Summary of geographical setting of included studies.\*

|  |  |  |
| --- | --- | --- |
|  | Publications | |
| Setting: | Number (n) | Percentage (%) |
| Low-income countries | 9 | 9 % |
| Lower-middle-income countries | 2 | 2 % |
| Upper-middle-income countries | 12 | 12 % |
| High-income countries | 73 | 71 % |
| Countries in different income groups | 7 | 7 % |
| Total | 103 | 100 % |

\* As defined by the World Bank for 2017.2

**TABLE S6** – Notes on the most frequent terms observed in the included publications.

|  |  |
| --- | --- |
| Term (Abbreviation) | Notes |
| “Immunological non-response” (INR) | INR was the most frequent term. The expression “non-response” is used to refer to a weak response and not exactly an absence of response, as most individuals present an unsatisfactory but existent immunological response after ART initiation. The abbreviation “INR” is frequently used for “international normalized ratio”, the standardized measure of oral anticoagulant effects. |
| “Discordant immunological response” (DIR) | DIR was the second most frequent term. This term may be misleading as it may refer to two different conditions: virologic-only response or immunologic-only response.3,4 |
| “Suboptimal CD4+ T-cell recovery” (SCR) | SCR was the third most frequent term. “Suboptimal” literally means “below the highest level”, which, in this case, excludes the optimal responses, but includes the poor and intermediate levels of immunologic response to ART. |
| “Poor CD4+ T cell recovery” (Poor CD4) and “poor immunological responders” (PIR) | “Poor CD4” and “PIR” were relatively frequent terms. Although the word “poor” may be perceived with a negative connotation and connected to the stigma and discrimination already associated with HIV infection,5 it literarily means “of a low or inferior standard or quality” (Oxford English Dictionary) or “less than adequate” (Merriam-Webster Dictionary), which is accurate for this condition. The expression “CD4+ T cell recovery” is more precise than “immunological response” in that it specifies the parameter used for analysis. “Poor CD4+ T cell recovery” is also used in the “Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV” from the United States Department of Health and Human Services,6 indicating internationally widespread use of this term beyond the scientific literature. Other terms were observed less frequently. |

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