

A systematic review of definitions of extreme phenotypes of HIV control and progression

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The study of individuals at opposite ends of the HIV clinical spectrum can provide invaluable insights into HIV biology. Heterogeneity in criteria used to define these individuals can introduce inconsistencies in results from research and make it difficult to identify biological mechanisms underlying these phenotypes. In this systematic review, we formally quantified the heterogeneity in definitions used for terms referring to extreme phenotypes in the literature, and identified common definitions and components used to describe these phenotypes. We assessed 714 definitions of HIV extreme phenotypes in 501 eligible studies published between 1 January 2000 and 15 March 2012, and identified substantial variation among these. This heterogeneity in definitions may represent important differences in biological endophenotypes and clinical progression profiles of individuals selected by these, suggesting the need for harmonized definitions. In this context, we were able to identify common components in existing definitions that may provide a framework for developing consensus definitions for these phenotypes in HIV infection.

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Introduction

Individuals with HIV infection show variable rates of disease progression and viral control. Whereas some subgroups of individuals control infection very well and

remain asymptomatic for several years, others show rapid immunological and clinical progression. A number of terms have been used to describe individuals at these extremes of the clinical spectrum, including 'long-term nonprogressors' (LTNPs) [1–5], 'elite controllers' [6,7],

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'slow progressors' [8–10], 'HIV controllers' (HICs) [11], 'viremic controllers' [1], 'noncontrollers' [12], and 'rapid progressors' [13–15]. These terms represent extremes within the virological and clinico-immunological range of disease, with LTNPs and rapid progressors lying on opposite extremes of the clinico-immunological distribution, and elite controllers and noncontrollers lying on opposite ends of the spectrum of viral control. The study of these individuals has provided valuable insights into the biology and pathogenesis of disease control and progression [5,16,17]. Indeed, elite controllers have been regarded as a natural model for disease control, and understanding the underlying biological mechanisms of this phenomenon could provide novel therapeutic targets [17,18].

Although these groups have been the focus of intense study, there is no consistency in how they have been defined. Studies suggest that different definitions may select for groups with varying clinical outcomes, and represent different biological endophenotypes [1,14,19]. This variability in definitions also has important implications for the design of future biological research in HIV and for the interpretation of results from existing literature. Recommendations for consensus definitions are needed. To examine variability in these definitions, we conducted a systematic review of the literature. Here, we describe heterogeneity in the definitions used, and identify common definitions that may provide a framework for developing consensus definitions for extreme HIV clinical phenotypes.

Methods

Search strategy

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20]. We used a combination of MeSH and non-MeSH terms representing extremes of virological and clinical progression in HIV in PubMed, and reviewed abstracts for all articles available between 1 January 2000 and 15 March 2012 (Fig. 1). Terms representing extremes of disease progression and control were included in the search strategy, as shown in Fig. 1. A total of 1639 abstracts were reviewed in order to shortlist relevant publications (Fig. 1, Supplementary Data 1, <http://links.lww.com/QAD/A411>). We further reviewed the full-text articles if the abstract or title mentioned an extreme phenotype term for disease progression or control in HIV infection and pertained to HIV infection in human adults. Extreme phenotypes in both HIV-1 and HIV-2 infection were considered for the purposes of this review. Articles were excluded if there was no mention of disease progression or control in the abstract or title, or if extreme phenotype definitions applied to children (<18 years of age) or to studies in animals. Articles were also reviewed if it was

unclear whether they met the inclusion or exclusion criteria for the analysis.

On reviewing 1639 abstracts, we identified 730 articles for full-text review, and 501 studies were included in the final analysis (Fig. 1, Supplementary Data 2, <http://links.lww.com/QAD/A412>). Full-text articles were reviewed for terms referring to extreme phenotypes in HIV infection, and definitions were entered into a database. We listed terms that described extremes of the clinical spectrum in HIV infection through this review. These included words and phrases used to describe extreme groups in each article, such as 'LTNPs', 'elite controllers', 'slow progressors', 'viremic controllers', 'rapid progressors', or 'noncontrollers' (Table 1). These phrases will hereby be referred to as 'terms', and represent variously defined phenotypes of HIV control and progression. The set of clinical and immunological criteria used to describe the terms in each study are referred to as 'definitions' (Table 2). The data obtained using the search strategy were independently reviewed by two investigators (DG and LI) to identify articles for inclusion and to assess observer bias. Data obtained by the two investigators were then synthesized and collated. Any discrepancies in results were resolved by a consensus discussion. The database was examined for any duplicate definitions and these were deleted.

Data retrieval

Definitions, as described above, were collated on an electronic database. Definitions were only included if they incorporated at least one quantitative element and pertained to extreme phenotypes in the context of the natural course of HIV infection. Purely conceptual definitions of phenotypes without any quantitative element and definitions pertaining to extremes of viral or immunological control following antiretroviral treatment were not included in the analysis. However, definitions were included if they referred to extremes in the natural progression of HIV infection or viral control, even if they did not explicitly specify individuals being antiretroviral therapy (ART)-naïve, as long as definitions did not pertain specifically to treatment-related viral control/disease progression phenotypes. Articles reviewing HIV phenotypes, listing several definitions, were not included. Studies describing case series with no defining criteria were not included in the analysis (Fig. 1, Supplementary Data 2, <http://links.lww.com/QAD/A412>).

When more than one definition was applied to a term, we listed this as two separate definitions in the database. Conversely, if more than one term was used to describe a group of individuals, definitions were listed under all terms used to refer to the individuals in the study. Therefore, the number of definitions may be different from the number of studies listed, as more than one term may appear in a single study and/or more than one definition may apply to a single term in a study. For

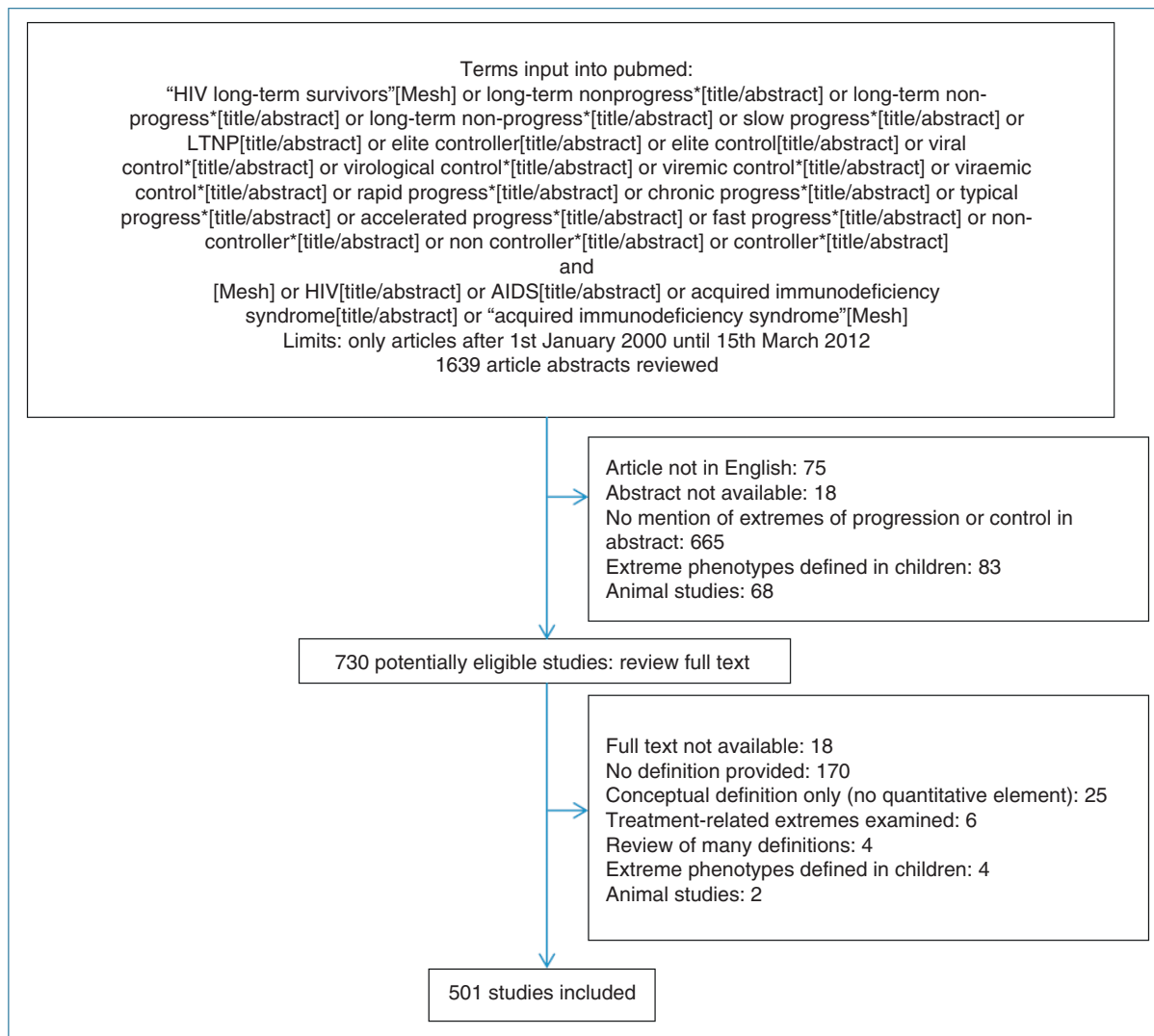


Fig. 1. Search strategy.

example, in one study, the terms ‘LTNPs’ and ‘slow progressors’ were used synonymously, and were defined as HIV-infected individuals who maintain CD4⁺ cell counts above 500/μl for at least 10 years after seroconversion or suppress viral replication to levels of HIV-1-RNA below 300 copies/ml and maintain CD4⁺ cell counts of at least 1000/μl for at least 6 years [21]. In this case, maintenance of CD4⁺ cell counts above 500 cells/μl for more than 10 years following seroconversion, and suppression of viral loads to below 300 copies/ml with maintenance of CD4⁺ cell counts above 1000 cells/μl for 6 years, were considered as separate independent definitions of long-term nonprogression/slow progression. In addition, both definitions were listed under the terms LTNPs and slow progressors separately, as both terms were used to describe this group. Thus, although these definitions pertained to one study, they were included as four separate data points in the review, two for LTNPs and two for slow progressors. Lists of collated definitions for all terms can be found in Supplementary Data 3 and

4, <http://links.lww.com/QAD/A414>, <http://links.lww.com/QAD/A413>.

Data synthesis

Of 1639 papers examined, 501 articles included definitions of terms used to describe extremes of disease progression or viral control. We listed all terms applying to definitions of extreme groups in the clinical/virological spectrum of HIV, and examined definitions within these groups. For the purposes of listing definitions, terms representing similar extreme groups were collapsed as shown in Table 1 and Fig. 2. For example, the term ‘slow progressors’ encompasses the terms ‘slow progressors’ and ‘long-term slow progressors’, and the term ‘elite controllers’ encompasses the terms ‘elite controllers’ and ‘elite suppressors’. Table 1 describes these individual terms, their frequency, and the terms collapsed under generic term labels.

To facilitate comparison of definitions, and explore heterogeneity among definitions and terms, we collapsed

Table 1. Frequency of occurrence of terms used to describe extreme phenotypes in HIV in the literature.

Slow progression	No.	Viral control	No.	Slow progression- viral control hybrid	No.	Rapid progressor	No.	Noncontroller	No.
Long-term nonprogressor (LTNP) ^a	264	Controller (C) ^d	8	Long-term nonprogressor-elite controller (LTNP-EC) ^g	5	Fast progressor (FP) ^h	11	High viral load individual	1
Clinical LTNP (CLTNP) ^a	1	HIV controller (HIC) ^d	46	Elite-LTNP (E-LTNP) ^g	1	Rapid progressor (RP) ^h	79	Medium-high viral load individual	2
Slow progressor (SP) ^b	70	Elite controller (EC) ^e	103	Long-term nonprogressor-viral controller (LTNP-VC)	1	Super fast progressor (SFP)	1	Noncontroller (NC)	16
Long-term slow progressor (LTSP) ^b	1	Elite suppressor (ES) ^e	14	Long-term nonprogressor-controller (LTNP-C)	1	Accelerated progressor (AP)	1	Viremic individual (VI)	3
Long-term survivor (LTS)	20	Natural viral suppressor (NVS) ^f	4	Nonprogressor-elite controller (NP-EC)	1				
Long-term asymptomatic (LTA)	4	Viral suppressor (VS) ^f	1	Viremic nonprogressor (VNP)	2				
Nonprogressor (NP) ^c	12	Low viral load individual (LVI)	2	Viremic noncontrollers (VNC)	1				
Clinical nonprogressor (CNP) ^c	1	Relative controller (RC)	2						
Slow progressor with robust replication (SP-RR)	1	Viremic controller (VC)	32						
		Aviremic individual (AVI)	2						

^aCollated under the term 'long-term nonprogressors'.^bCollated under the term 'slow progressors'.^cCollated under the term 'nonprogressor'.^dCollated under the term 'HIV controller'.^eCollated under the term 'elite controller'.^fCollated under the term 'natural virus suppressor'.^gCollated under the term 'elite-LTNP'.^hCollated under the term 'rapid progressor'.

Table 2. Glossary of descriptors used in review.

	Definitions
Terms	Words or phrases describing extremes of the clinico-immunological and virological spectrum in HIV infection, e.g., 'elite controllers'.
Definitions	The set of clinical and immunological criteria used to describe the terms in each study. For example, elite controllers are HIV-infected individuals who suppress plasma HIV-RNA levels to <50 copies/ml without antiretroviral treatment.
Component	Broad categories of common clinical and immunological criteria used in definitions. For example, 'HIV-RNA level' is a component of definitions for elite controllers
Component threshold/category	Thresholds or categories for the specific component in each definition. For example, a HIV-RNA threshold of <50 copies/ml in definitions of elite controllers

definitions that contained common components and component thresholds for clinical and immunological criteria under each term (Table 3). These broad components were identified by reviewing all definitions for each term. The term 'component' here refers to categories of common clinical and immunological criteria used in definitions, and 'component threshold/categories' refers to the thresholds or categories used for these components in each definition (Table 2). For example, key components identified for definitions of

LTNPs were duration of follow-up, CD4⁺ cell count threshold, HIV-RNA thresholds, CD4⁺ cell slopes and clinical criteria, such as asymptomatic or AIDS-free follow-up (Table 3). To identify unique definitions for each term, we then collapsed definitions based on each distinct combination of components and component thresholds or categories, with a view to grouping broadly similar definitions. We only collapsed definitions for terms for which we had identified more than 10 definitions in the literature. When different duration

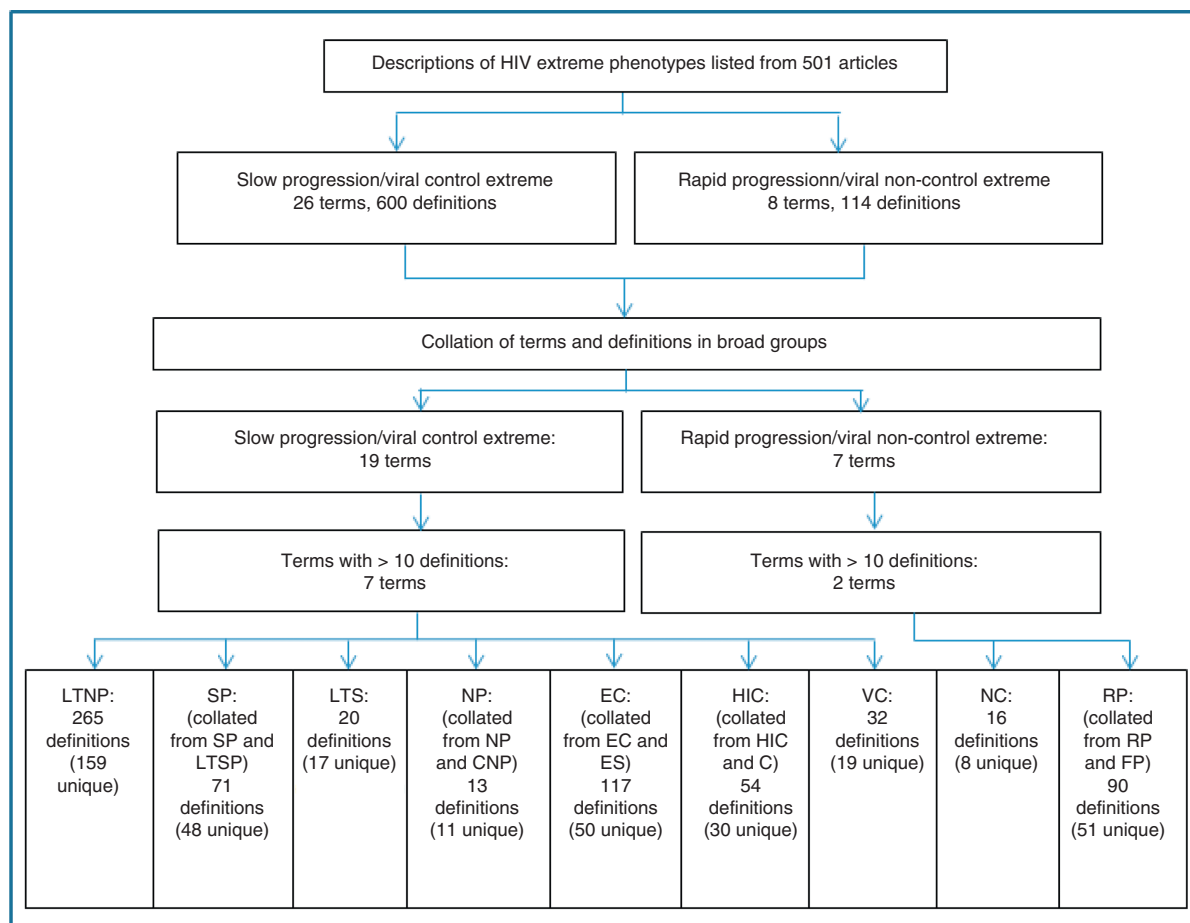


Fig. 2. Data synthesis: a process for collapsing and categorizing individual terms and definitions. C, controller; CNP, clinical nonprogressor; EC, elite controller; ES, elite suppressor; FP, fast progressor; HIC, HIV controller; LTNP, long-term nonprogressor; LTS, long-term survivor; LTSP, long-term slow progressor; NC, noncontroller; NP, nonprogressor; RP, rapid progressor; SP, slow progressor; VC, viremic controller.

Table 3. Broad components used to collapse definitions of progression and control HIV phenotypes.

Components of slow progression/viral control phenotype definitions (terms – LTNP, SP, LTS, NP, EC, HIC, and VC)		Components of rapid progression/viral noncontrol phenotype definitions (terms RP and NC)	
Components	Component threshold/category	Component	Component threshold/category
Duration of follow-up	Minimum duration of follow-up in years	Duration of follow-up	Minimum duration of follow-up in years
CD4 ⁺ cell count	CD4 ⁺ cell count threshold in count/μl	CD4 ⁺ cell endpoint	CD4 ⁺ cell count threshold in count/μl
HIV-RNA level	Plasma HIV-RNA threshold in copies/ml	HIV-RNA level	Plasma HIV-RNA threshold in copies/ml
Clinical symptoms	Asymptomatic/AIDS-free/OI free (yes/no)	CD4 ⁺ cell slope	Numeric threshold of decline in cells/μl per year
CD4 ⁺ cell slope	Numeric threshold of decline in cells/μl per year or qualitative (e.g., ‘stable’ CD4 ⁺ cell levels)	AIDS endpoint	AIDS endpoint present in definition (yes/no)
Viral blips	Threshold for occasional spikes in HIV-RNA levels allowed	ART endpoint	ART endpoint present in definition (yes/no)
		Death endpoint	Death endpoint present in definition (yes/no)
		Seroconversion status	Seroconversion status known (yes/no/unspecified)

ART, antiretroviral therapy; EC, elite controllers; HIC, HIV controllers; LTNP, long-term nonprogressors; LTS, long-term survivors; NC, noncontrollers; NP, nonprogressors; OI, opportunistic infection; RP, rapid progressors; SP, slow progressors; VC, viremic controllers.

thresholds were applied to different components in a definition (e.g., duration of asymptomatic follow-up, duration of CD4⁺ cell level below a threshold), only the greatest duration was considered, as this would be the minimum duration of follow-up needed to meet the criteria for a given definition. When multiple HIV-RNA assays were used, the assay with the highest threshold for lower limit of detection was considered.

After collapsing, definitions with a distinct combination of components and component thresholds/categories were identified as being unique. The proportion of unique definitions was calculated for each term. This proportion reflects the heterogeneity of definitions in literature. We ranked definitions identified in this way by frequency of occurrence, and listed the most common definitions for each term. The salient features of each definition were listed based on common components identified across definitions, to describe the most common components used to define terms referring to HIV extreme phenotypes in the literature. We also compared the frequency of component thresholds used in definitions of different terms, in order to assess the overlap of components and component thresholds/categories between definitions of different terms.

Results

On reviewing 501 articles, 600 definitions were listed for 26 terms used to describe slow progression/viral control extremes in HIV infection and 114 definitions for eight terms used to define fast progressor/viral noncontrol extremes in HIV infection (Fig. 2). The various terms used to describe these extremes in the literature are outlined in Table 1. Following collapsing of terms under broad groups, 19 terms for slow progression/viral control phenotypes and seven terms for rapid progression/noncontrol phenotypes were examined (Table 1, Fig. 2).

Of the 26 terms listed, only nine terms that included more than 10 definitions each, were considered for further analysis (Fig. 2). The most common terms used in studies of slow progression extremes were ‘LTNP’ (265 instances), followed by ‘slow progressor’ (71 instances; Table 1), ‘long-term survivor (LTS)’ (20 instances), and ‘nonprogressors’ (13 instances). Common terms used to describe the extreme of viral control were ‘elite controllers/elite suppressors’ (117 instances), ‘viremic controller’ (32 instances), and ‘HIC/controller’ (54 instances; Table 1). Fewer terms were identified for the rapid progression extremes in HIV infection, with 90 instances of ‘rapid progressors/fast progressors’ (Table 1). For the extreme of noncontrol of HIV, ‘noncontroller’ was the commonest term used, with 16 definitions appearing in the literature.

We also examined the pattern of term usage by time of publication. We observed a greater diversity of terms used to describe viral control and noncontrol phenotypes in the period 2006–2012 as compared to the literature published between 2000 and 2005 (Fig. 3). Notably, terms pertaining to viral control phenotypes, such as ‘elite controller’, ‘HIC’, ‘viremic controller’, and ‘noncontroller’ seem to be used almost exclusively from 2006 onward, indicating the more recent interest in viral control-related phenotypes as compared with clinical phenotypes of nonprogression or rapid progression in the literature.

Redundancy of definitions in the literature

The total number of definitions and the number of unique definitions identified for each term are presented in Table 4. Heterogeneity in definitions was high, with a large proportion of definitions being unique for progression (54–85%) and viral control (43–59%)–related terms. Unique definitions for all terms can be found in

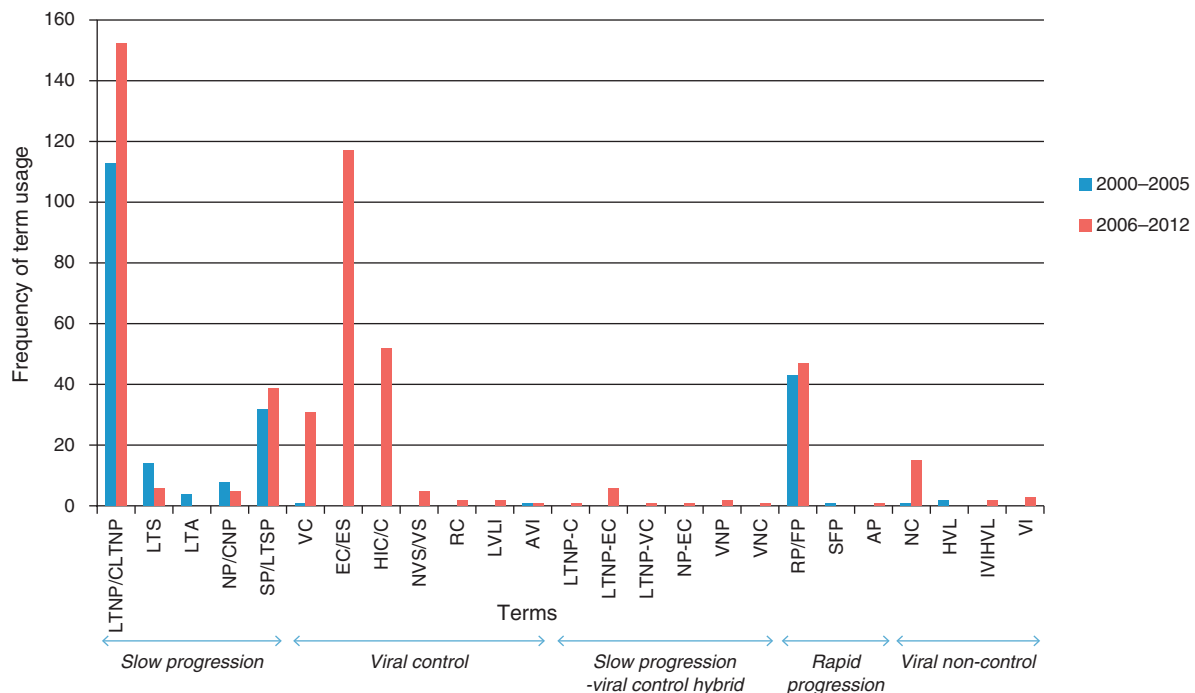


Fig. 3. Frequency of term usage by calendar period. AP, accelerated progressor; AVI, aviremic individual; C, controller; CLTNP, clinical long-term nonprogressor; CNP, clinical nonprogressor; EC, elite controller; ES, elite suppressor; FP, fast progressor; HIC, HIV controller; HVL, high viral load individual; LTA, long-term asymptomatic; LTNP, long-term nonprogressor; LTNP-C, long-term nonprogressor controller; LTNP-EC, long-term nonprogressor-elite controller; LTNP-VC, long-term nonprogressor-viremic controller; LTS, long-term survivor; LTSP, long-term slow progressor; LVLI, low viral load individual; MHVL, medium-high viral load individual; NC, noncontroller; NP, nonprogressor; NVS, natural viral suppressor; RC, relative controller; RP, rapid progressor; SFP, super fast progressor; SP, slow progressor; VC, viremic controller; VI, viremic individual; VNC, viremic noncontroller; VNP, viremic nonprogressor; VS, viral suppressor.

Supplementary Tables 1–9, <http://links.lww.com/QAD/A415>.

Description of extreme phenotypes in the literature

Long-term nonprogressors

Of 265 definitions of LTNPs, 159 were unique when combinations of duration of follow-up, CD4⁺

cell thresholds, CD4⁺ cell slopes, clinical symptoms, and viral load components were considered. There was substantial variation in components and component thresholds (Fig. 4, Supplementary Table 10, <http://links.lww.com/QAD/A415>). Duration of follow-up varied between 1 and 25 years among definitions, with 10 years being the most common duration of follow-up required (Fig. 4). Although CD4⁺ cell thresholds were a prominent feature of LTNP definitions, with 74% of all definitions including a CD4⁺ cell threshold criterion, thresholds showed marked variation across definitions with a range between 300 and 1000 cells/ μ l. The most

Table 4. Proportion of unique definitions within each term.

Phenotype	Terms	Total number of definitions	Unique definitions (%)
Slow progression	LTNP	265	159 (60%)
	SP	71	48 (69%)
	LTS	20	17 (85%)
	NP	13	11 (85%)
Viral control	EC	117	50 (43%)
	HIC	54	30 (56%)
	VC	32	19 (59%)
	RP	90	51 (54%)
Rapid progression	NC	16	8 (50%)
Viral noncontrol			

EC, elite controller; HIC, HIV controller; LTNP, long-term nonprogressor; LTS, long-term survivor; NC, noncontroller; NP, nonprogressor; RP, rapid progressor; SP, slow progressor; VC, viremic controller.

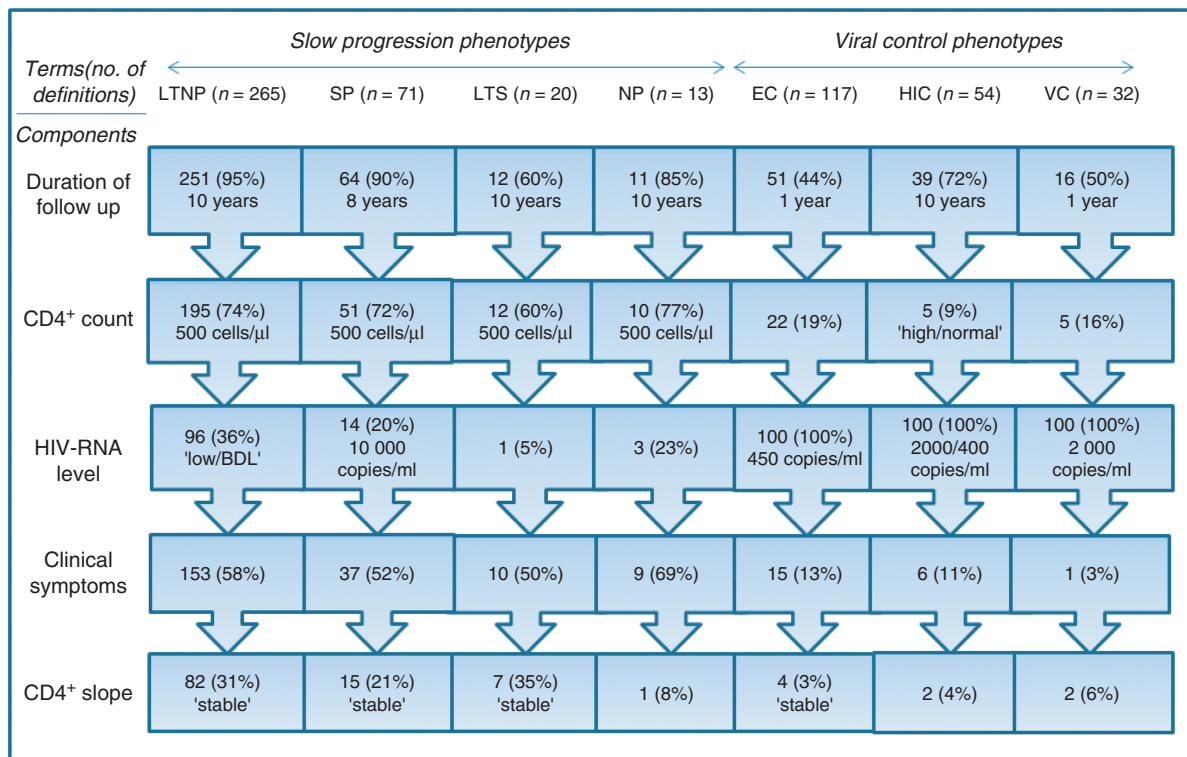


Fig. 4. Predominant components and common thresholds used in definitions of slow progression/viral control terms in HIV infection. The figure depicts the number of definitions (with proportions in parentheses) for slow progressor/viral control terms that include specific components and component thresholds as part of the definition. The most frequent component threshold applied for each of these also represented, where a single common threshold could be identified. BDL, below detection limit; EC, elite controller; HIC, HIV controller; LTNP, long-term nonprogressor; LTS, long-term survivor; NP, nonprogressor; SP, slow progressor; VC, viremic controller.

frequent CD4⁺ cell threshold was 500 cells/ μ l (Fig. 4, Supplementary Table 10, <http://links.lww.com/QAD/A415>). A component including a HIV-RNA threshold was less common, with only 36% of definitions including a viral load criterion. The absence of clinical symptoms also appeared to be a prominent criterion, with around 58% of definitions including a criterion of being asymptomatic, without opportunistic infection or AIDS-free. CD4⁺ cell slopes were also common features of definitions, with 31% of definitions including a criterion for stability of CD4⁺ cell counts (Fig. 4).

Slow progressors

Of 71 definitions identified for slow progressors, 69% were unique with respect to the components described (Table 4). As with LTNP definitions, duration of follow-up was an important component, with 90% of definitions including a criterion for minimum duration of follow-up (Fig. 4). There was marked variation in duration thresholds, ranging from 10 months to 16 years, the most frequently appearing threshold being 8 years of follow-up (Fig. 4, Supplementary Table 10, <http://links.lww.com/QAD/A415>). In general, the duration of follow-up needed to define slow progressors was lower than that for LTNPs (Supplementary Table 10, [http://](http://links.lww.com/QAD/A415)

links.lww.com/QAD/A415). CD4⁺ cell thresholds and the absence of clinical symptoms were also important components, with 72 and 52% of definitions including these, respectively (Fig. 4). As with LTNPs, a CD4⁺ cell threshold of 500 cells/ μ l was most common, with thresholds ranging from 200 to 1000 cells/ μ l (Supplementary Table 10, <http://links.lww.com/QAD/A415>). The frequency of various component thresholds can be found in Supplementary Table 10, <http://links.lww.com/QAD/A415>. CD4⁺ cell slope and HIV-RNA thresholds were less common for these definitions, with only 21 and 20% of definitions including each of these components, respectively (Fig. 4).

Long-term survivors

Of 20 definitions listed for LTSs, 17 were unique (Table 4). As expected, duration of follow-up was a prominent component with 10 years being the most frequent threshold (Supplementary Table 10, <http://links.lww.com/QAD/A415>). CD4⁺ cell thresholds were also prominent components, with 12 definitions including a threshold, the commonest being 500 cells/ μ l (Table 4). Clinical criteria of symptom/AIDS-free follow-up were also common with 50% of definitions including this component (Table 4, Supplementary

Table 10, <http://links.lww.com/QAD/A415>). HIV-RNA levels and CD4⁺ cell slopes appeared to be less prominent components in these definitions.

Nonprogressors

A total of 13 definitions were identified for nonprogressors, of which 11 were unique (Table 4). Duration of follow-up and CD4⁺ cell threshold components were prominent in this group, with 10 years and 500 cells/ μ l being the most common thresholds, respectively. HIV-RNA levels, clinical criteria, and CD4⁺ cell slopes only appeared in a minority of definitions (Fig. 4).

Elite controllers

A total of 117 definitions were identified for elite controllers, of which 50 were unique (Table 4). As expected from the terminology, HIV-RNA thresholds appeared in all definitions listed, with thresholds ranging from 40 to 500 copies/ml (Fig. 4, Supplementary Table 10, <http://links.lww.com/QAD/A415>). The most frequent HIV-RNA threshold used was 50 copies/ml. Only five definitions included a criterion for occasional blips in viral load (Fig. 4). Duration of follow-up also appeared to be important with 44% of definitions including a minimum duration of follow-up criterion. Duration thresholds varied from 6 months to 16 years, with a threshold of 1 year being most frequent (Supplementary Table 10, <http://links.lww.com/QAD/A415>). CD4⁺ cell thresholds appeared only in 19% of definitions, in contrast with LTNPs and slow progressors, wherein 74 and 72% of definitions included this component.

HIV controllers

A total of 54 definitions for HICs were identified, of which 56% were unique (Table 4). All definitions included a HIV-RNA threshold (Fig. 4). HIV-RNA thresholds varied from 40 to 10 000 copies/ml, with 400

and 2000 copies/ml both being common thresholds applied (Supplementary Table 10, <http://links.lww.com/QAD/A415>). Duration of follow-up was also an important component of these definitions, with 72% of definitions including a cut-off for the minimum duration of follow-up required (Fig. 4). Thresholds of 10 years and 1 year appeared to be most common for these definitions, which can be seen as a product of the two most common definitions of this term (Supplementary Table 10, <http://links.lww.com/QAD/A415>, Table 5).

Viremic controllers

Of 32 definitions applied to viremic controllers, the majority (59%) were unique, suggesting marked variability in definitions used (Table 4). As with elite controllers and HICs, all definitions included a HIV-RNA threshold (Fig. 4). Thresholds were generally higher in comparison with elite controller definitions and varied between 500 and 15 000 copies/ml, with a threshold of 2000 copies/ml being most common (22/32 definitions; Supplementary Table 10, <http://links.lww.com/QAD/A415>). CD4⁺ cell thresholds appeared as components in five of 30 definitions, and there was marked variability in thresholds used (Supplementary Table 10, <http://links.lww.com/QAD/A415>). As with elite controllers and HICs, clinical criteria only appeared in a minority of definitions.

Rapid progressors

Of 90 definitions identified for the terms 'rapid progressor' or 'fast progressor', 51 definitions were unique based on combinations of components considered (Table 4). CD4⁺ cell thresholds and AIDS endpoints appeared to be the most common components of definitions, with 56% of definitions including a CD4⁺ cell endpoint, and 48% of definitions including an AIDS endpoint (Fig. 5). Among CD4⁺ cell endpoints, a threshold of 300 cells/ μ l was the most frequent (Fig. 5,

Table 5. Common definitions identified for common terms used to describe extremes in HIV infection.

Term	Commonest definition ^a	Frequency
LTNP	Asymptomatic and ART-naïve for 10 years during follow-up with all CD4 ⁺ cell counts above 500 cells/ μ l during this period	15/265
SP	Seropositive asymptomatic individuals infected for 8 or more years with a CD4 ⁺ T-cell count above 500 cells/ μ l in the absence of ART.	16/71
EC	Spontaneously maintain viral loads below 50 copies/ml without ART	33/117
HIC	HIV-infected patients who had been seropositive for >10 years and had received no ART for whom >90% of the HIV-RNA measurements were <400 copies/ml Alternate definition: HIV-infected individuals with at least three measurements of plasma HIV-RNA <2000 copies/ml over at least a 12-month period in the absence of ART	8/54 7/54
VC	Infected with HIV and maintaining viral loads of <2000 RNA copies/ml without ART	4/32
RP	HIV infected with CD4 ⁺ T-cell counts of <300 cells/ μ l within 3 years after the last HIV-seronegative test	17/90
NC	HIV-infected individuals with plasma HIV-RNA >10 000 copies/ml without ART	6/16

ART, antiretroviral therapy; EC, elite controller; HIC, HIV controller; LTNP, long-term nonprogressor; NC, noncontroller; RP, rapid progressor; SP, slow progressor; VC, viremic controller.

^aSingle dominant definitions could not be identified for long-term survivors and nonprogressors and are, therefore, not presented here.

Supplementary Table 11, <http://links.lww.com/QAD/A415>). Time to end-point was a prominent component of definitions, with 92% of definitions including a duration component, the most frequent threshold being 3 years (Fig. 5, Supplementary Table 11, <http://links.lww.com/QAD/A415>). Known date of seroconversion appeared to be a prominent component, with 80% of definitions including this (Fig. 5). However, many definitions did not specify time since seroconversion, including either time from diagnosis or only CD4⁺ cell slope-based criteria. HIV-RNA thresholds were rare (6%) among these definitions (Fig. 5). Death and ART initiation were also used as endpoints in a small number of definitions (3% each).

Noncontrollers

There were only 16 definitions of noncontrollers listed, of which eight were found to be unique based on combinations of components (Table 4). All definitions included a HIV-RNA component, with 10 000 copies/ml being the most common cut-off used (Fig. 5). CD4⁺ cell endpoints were also used in two definitions (Fig. 5, Supplementary Table 11, <http://links.lww.com/QAD/A415>).

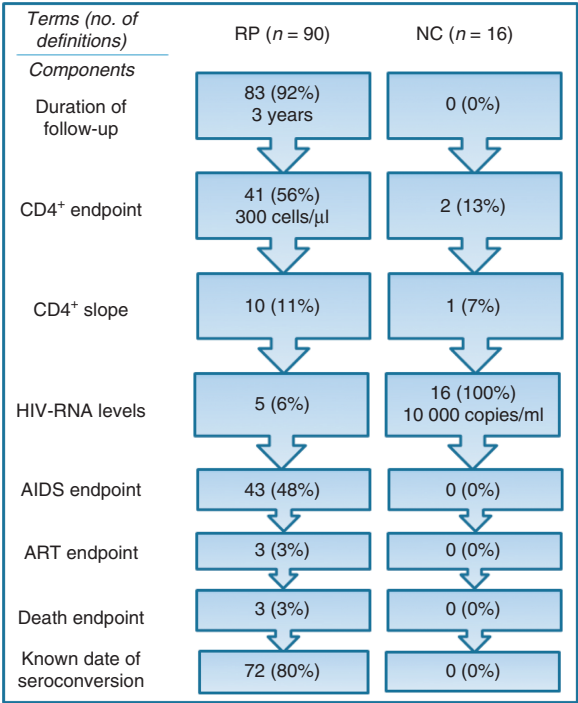


Fig. 5. Predominant components and common thresholds used in definitions of rapid progression/noncontroller terms in HIV infection. The figure depicts the number of definitions (with proportions in parentheses) for rapid progressor/non-controller terms that include specific components and component thresholds. The most frequent component threshold applied for each of these also represented, wherein a single common threshold could be identified. NC, noncontroller; RP, rapid progressor.

A415), but no clinical endpoints appeared in any definition.

Common definitions of HIV phenotypes

The most frequently occurring definitions for each term are listed in Table 5. Single dominant definitions that were clearly much more common than others could be identified for most terms, except HICs for whom two common definitions were identified (Table 5). Although common definitions are clearly identified for each term, it can be seen that these still represent the minority of all definitions listed (Table 5). It is also clear that, although there are marked differences in the components of definitions for each term, in most cases specific component thresholds can be identified for each term that are far more common than others (Figs. 4 and 5). Using the most common components and component threshold/category within components to derive common definitions produced identical results to those produced by grouping individual definitions (Figs. 4 and 5 and Table 5). For example, the most common definition for LTNP was an HIV-infected individual who is asymptomatic and ART-naïve for 10 years during follow-up with all CD4⁺ cell counts above 500 cells/μl during this period, which combines the most common components and component thresholds/categories listed for definitions of this term (Fig. 4).

Overlap between definitions

There was substantial overlap between components across terms, with 36% of LTNP definitions including HIV-RNA threshold criteria and 19% of elite controller and 16% of viremic controller definitions including CD4⁺ cell threshold components (Fig. 4). There was marked overlap between components and thresholds/categories used across all slow progression terms, with substantial overlap between components of LTNPs, slow progressors and nonprogressors, and between viremic controller and HICs (Supplementary Table 10, <http://links.lww.com/QAD/A415>).

Broad phenotypes represented by different terms

On the basis of our review, we sought to characterize the broad HIV phenotypes represented by different terms in the literature. On considering components and component thresholds/categories of definitions for slow progression-related terms, the clinical phenotypes

represented by LTNPs, LTSs, and nonprogressors were broadly similar, and represented individuals who maintained normal CD4⁺ cell counts, and remained healthy at least for 10 years of observed follow-up. In general, slow progressors represented a less stringent phenotype, and thresholds for duration of follow-up required tended to be lower (Supplementary Table 10, <http://links.lww.com/QAD/A415>). The relative representation of viral control phenotypes could be broadly characterized, with elite controllers representing the most extreme phenotype of viral control, and viremic controllers representing higher levels of viremia (Fig. 6). For HICs, two broad phenotypes seemed to predominate: one appeared to be similar to elite controllers, but with control of viremia to below 400 copies/ml over at least 10 years, and the second encompassing elite controller and viremic controller phenotypes (Fig. 6).

Discussion

In this systematic review, assessing 714 definitions of HIV extreme phenotypes in 501 eligible studies, we identified substantial variation among definitions used to describe

extreme phenotypes in HIV infection. This heterogeneity in definitions may represent important differences in biological endophenotypes [14] and clinical progression profiles [1,22] of individuals selected by these, suggesting the need for harmonized definitions. In this context, we were able to identify common components in existing definitions that may provide a framework for developing consensus definitions for HIV extreme phenotypes.

Although recent studies have focused on extreme phenotypes in HIV infection as natural models of viral control and the extremes of disease progression in HIV, little is known about the impact of heterogeneity in definitions on clinical and biological phenotypes captured. This heterogeneity has implications for the design of studies exploring HIV biology and for the interpretation of existing research. Although several studies have referred to this marked variation in definitions, and the need for standardized phenotype definitions [2,22], the full extent of variability in the literature has never been formally quantified. To our knowledge, this is the first study that has attempted to address this in a systematic manner. Formal evaluation of the impact of varying definitions on clinical outcomes and characterizing biological endophenotypes is essential to develop

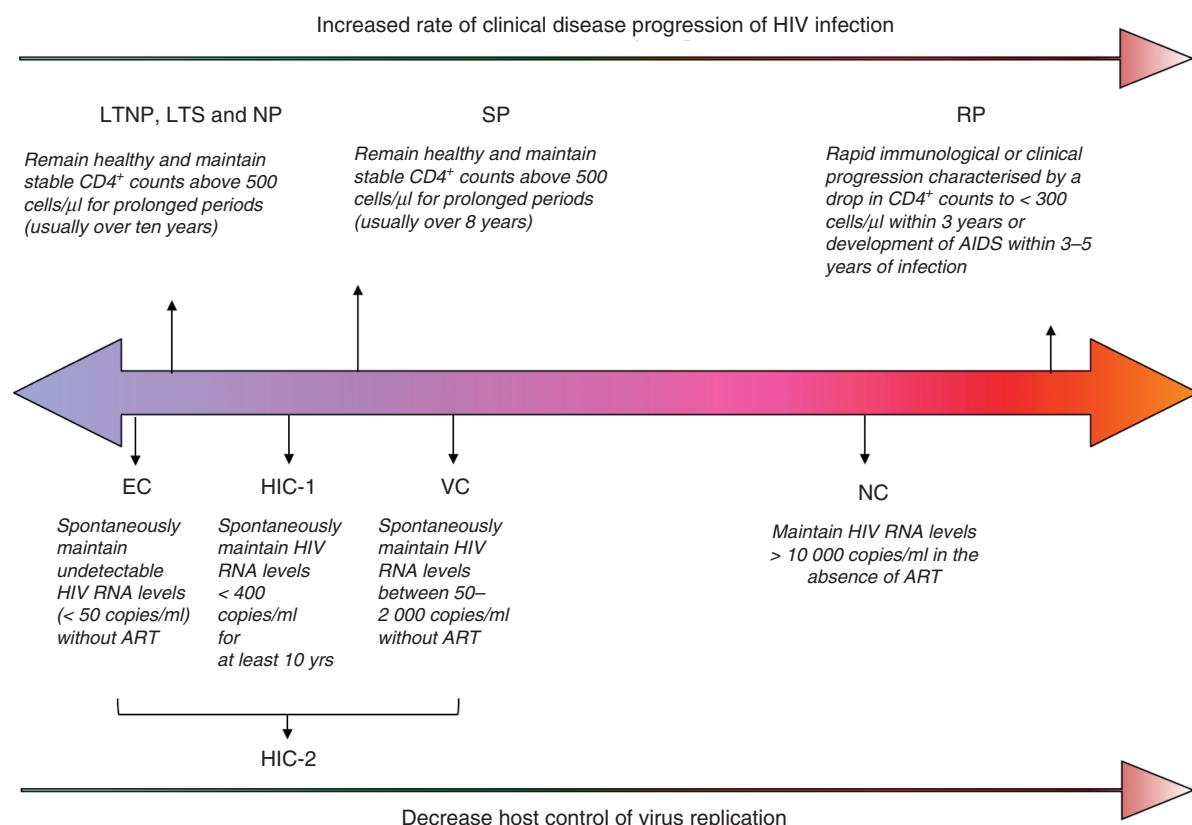


Fig. 6. Relative characteristics of phenotypes referred to by different terms in the literature. HIC-1 and HIC-2 refer to the two most commonly used definitions for HIV controllers. ART, antiretroviral therapy; EC, elite controller; HIC, HIV controller; LTNP, long-term nonprogressor; LTS, long-term survivor; NC, noncontroller; NP, nonprogressor; RP, rapid progressor; SP, slow progressor; VC, viremic controller.

harmonized definitions that will represent clinical and biological phenotypes of interest.

Understanding the impact of variability in phenotype definitions on clinical outcomes in HIV is important, as the literature suggests that small variations in phenotype definitions can substantially impact the trajectory of disease progression in patients selected. In one study, varying the duration of follow-up threshold for LTNP resulted in the selection of groups with markedly different survival times [1]. A recent study showed that allowing for at least one nadir CD4⁺ cell count below 500 cells/ μ l among LTNPs can lead to a significant reduction in the time to disease progression compared with individuals who maintain all CD4⁺ cell counts above this threshold [22]. This is consistent with research within the French Hospital Database that showed that a positive CD4⁺ cell slope was a more selective criterion than a longer duration of HIV infection (10 years instead of 8 years), for selecting patients who were asymptomatic and ART-naïve several years after being infected by HIV [2]. Similar findings have been demonstrated with viral control phenotypes; individuals with viral loads less than 50 copies/ml (elite controllers) have markedly improved AIDS-free survival compared with individuals with viral loads between 50 and 2000 copies/ml [1]. Prevalence of phenotypes represented can also vary markedly with small changes in definitions. For example, in the French Hospital Database, increasing the CD4⁺ cell threshold in LTNPs from 500 to 600 cells/ μ l changed the prevalence of the phenotype from 22 to 11% in the cohort, and addition of a criterion for positive CD4⁺ cell slope further reduced the prevalence to 2.8% [2]. This is of particular relevance to studies that aim to recruit individuals with extreme phenotypes for further characterization of mechanisms of immune-virological control.

Variation in extreme phenotype definitions may also impact on the underlying biological endophenotype being examined. Our study suggests that there is marked overlap between components of definitions referring to different terms in the literature, which makes it difficult to delineate phenotypes represented by different terms. It is important to distinguish these terms in the literature, as different phenotypes may capture different underlying biology. Indeed, it has been shown that protective and high-risk alleles known to be associated with disease control and progression in HIV infection, show a graded change in frequency along the clinical spectrum of disease [14]. The limited overlap between LTNP and EC phenotypes in some studies, with only 8–32% of LTNPs meeting criteria for elite control [2,22,23], suggests that slow progression and viral control phenotypes are only modestly correlated, and may potentially represent distinct biological phenotypes. A recent genome wide association study further substantiated this with the discovery of a new locus associated with LTNP, when individuals who were EC (HIV-RNA levels

<100 copies/ml) were excluded from the cohort [19], suggesting that the determinants of viral control and slow progression phenotypes may be distinct.

Major strengths of our study include the comprehensive search strategy applied and the large number of articles reviewed. As the correlation between the studies short-listed for review by the two reviewers was high (>95%), there is unlikely to be substantial observer bias in the review process. We acknowledge that our review of definitions also has several limitations. Our search strategy was only restricted to one search engine, to published articles, and to articles available after the 1 January 2000, which may have limited the sensitivity of the search. Additionally, we did not examine definitions by differences in HIV subtypes and clades, and extreme phenotypes represented by definitions in these groups may differ. In spite of these limitations, we believe that our review is a fair representation of the heterogeneity in definitions observed in the literature, and the lower sensitivity of the review would only underestimate existing heterogeneity among definitions. Moreover, to our knowledge, this is the first attempt to formally characterize the variability in definitions of these terms in literature, and identify common components used to define these terms.

Given the possible differences in biological and clinical phenotypes captured by different definitions, it is important to standardize case definitions of these phenotypes for consistency in methods and ease of interpretation across studies. Although the various studies described have provided clues to the clinical and biological correlates of different definitions, the literature examining this is limited and further research specifically addressing variation in these phenotypes with varying definitions of phenotypes is essential to develop a framework for consensus definitions.

Several attributes of definitions must be considered when formulating consensus definitions. First, phenotype definitions should capture a truly extreme phenotype, as sampling from extremes can be a powerful way to examine HIV biology. This approach has been shown to be effective [19,24,25] in identifying genetic variants associated with HIV control and progression. Second, definitions should represent biologically relevant endophenotypes, so that underlying biology associated with these can be examined efficiently. Further research specifically examining the heritability and underlying biology of different phenotypes is needed in order to establish which phenotypes are likely to be most biologically relevant. Third, the phenotype definition should include components that are clinically relevant and adequately stable to predict long-term clinical outcomes. It is also important that the components described can be easily assessed and data for these can be readily extracted from existing cohorts. This would require systematic

assessment of clinical outcomes of commonly used definitions in large-scale consortia, which have adequate numbers of these rare individuals, and appropriate data on seroconversion and detailed clinical outcomes. While ascertaining the most useful definitions for extreme HIV phenotypes is challenging, our study shows that in spite of the large amount of heterogeneity observed in definitions, common components and thresholds used in definitions can be identified for most terms, indicating that there are common threads that have been used to define these groups in the literature, which could provide the framework for consensus definitions. Further work specifically examining the biological characteristics and differences in clinical progression, among these groups of individuals is needed in order to inform the utility of different definitions in HIV research.

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Conflicts of interest

There are no conflicts of interest.

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