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Towards standardized definitions for monitoring the continuum of HIV care in Europe

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Introduction

The continuum of HIV care is a simple conceptual framework for monitoring HIV programmes, comprising a series of stages that people living with HIV (PLHIV) pass through to access antiretroviral treatment (ART) and achieve viral suppression [1,2]. Individual benefits of suppression include reduced risk of morbidity and mortality. At the population level, viral suppression reduces the risk of onward transmission and enables epidemic containment [3]. Transmission risk may be further reduced by lowering the number of undiagnosed PLHIV [4,5]. Complete continua are, therefore, constructed beginning with the total number of PLHIV in a given population and ending with the number virally suppressed. Intervening stages have included the numbers diagnosed, linked to HIV care, retained in care, eligible for ART, on ART and adhering to ART. Although people can move between stages, the continuum is typically conceptualized as a ‘snapshot’ at one time-point.

As the Joint United Nations Programme on HIV and AIDS (UNAIDS) announced the target of reaching ‘90–90–90’ by

2020, which envisions 90% of PLHIV diagnosed, 90% of those diagnosed on ART and 90% of those on ART virally suppressed [6], interest in constructing HIV care continua to inform national programmes and policies has grown [7–11]. However, there has been limited consistency in the methods used to construct these measures and the stages presented in publications. Key stages are often missing or continua entirely absent for many countries, including in Europe, particularly the Eastern region [7,8,11–15]. Drawing from a review of recent literature and expert opinion, we highlight the methodological inconsistencies, the challenges associated with constructing each stage and recommend a standardized way forward for monitoring the continuum of HIV care in Europe.

Methodological inconsistencies and challenges

Despite the simplicity of the care continuum concept, complexities in its construction have generally been

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overlooked [16]. Methodological differences make it difficult to compare estimates between countries or to combine data to produce regional or global estimates [13]. Initial attempts have been made to standardize definitions in Europe [17] and globally [11,18,19], though further support is needed [13].

The first stage, the total number of PLHIV, is the crucial denominator against which all subsequent estimates are measured. Yet, it is often ignored or omitted because of methodological challenges in its estimation [7,8,20]. In continua in which it is included, estimation methods are diverse, with each of thirteen continua included in a recent systematic review by using a different data source and methodology to estimate this stage [7].

Unlike stage 1 which, by definition, must be estimated, subsequent stages can be directly observed given complete surveillance. As such, stage 2, the population diagnosed, is more frequently reported and definitions are more consistently applied [20]. Most frequently, all individuals ever diagnosed since the beginning of the epidemic and still alive are included, although a minority of continua apply a narrower time window and several have difficulties excluding deaths or out-migrations [12,20].

Definitions for linkage to and retention in care are particularly diverse [8,12,20,21]. Being linked to care may include anyone enrolled in a clinical cohort, or those who started receiving care within a specific time frame following diagnosis [12,21–23]. A variety of measures of ‘receiving care’ are used to define linkage or retention, such as the availability of CD4⁺ cell counts, viral loads, other laboratory measurements or recorded clinic visits [12,22]. Such differences reflect the diversity in health systems, frequency of follow-ups and data availability in each country [13], which renders these stages incredibly challenging to standardize or monitor at a European level, leaving some countries unable to measure them at all [13]. Misclassification of patients at these stages will also affect estimates for dependent downstream stages [24,25].

Inconsistencies in the definitions of ‘being on ART’ include estimates based on prescribed or dispensed drugs [7], exclusion of mono-drug or dual-drug regimens [26] or of those who discontinued therapy [12], or applying a minimum time on ART [13]. Moreover, the term ‘on ART’ is imprecise, as continua rarely measure adherence to treatment [8,21]. In some cases, in which prevailing guidelines recommend ART initiation below specific CD4⁺ cell count thresholds, the proportion on ART is restricted to those eligible for treatment [8,27].

For the final stage, thresholds used to define viral suppression differ, as does the timing of measurement, for example last or any suppressed viral loads [7,8,12,13,16,21], although this detail is often omitted [7,28].

Towards a standardized four-stage HIV care continuum

We recommend that European countries focus efforts on constructing and reporting the following four priority stages: stage 1, the number of PLHIV; stage 2, the number/proportion diagnosed; stage 3, the number/proportion on ART; and stage 4, the number/proportion virally suppressed (Table 1). These four stages accord with the UNAIDS 90–90–90 target and, measured as a ‘snapshot’, or cross-section in time, are most important from a public health perspective to infer the number with detectable viral loads with the potential for transmitting HIV. Our recommendations reflect a consensus reached by a broad group of European experts convened by the European Centre for Disease Prevention and Control (ECDC) to discuss optimal approaches to constructing HIV-care continua [22]. They are also consistent with frameworks recently applied and opinions emerging at a global level [8,12,13,20]. Further work is required to develop guidance for measuring linkage to and retention in care, as these intervening stages are important quality of care indicators and process measures, although the diversity in data sources and definitions remains a barrier to standardization at this time.

The denominator of PLHIV should include all HIV-positive individuals, diagnosed and undiagnosed, living in the country at the end of a given year. Likewise, stage two, by definition depends on the first stage and should, therefore, ideally be the proportion of PLHIV ever diagnosed, including in-migrations and excluding deaths and out-migrations by the end of the given year. This is inherently challenging, as it relies on cumulative HIV surveillance data since the beginning of the epidemic, linked to reliable death and migration data, or complete case surveillance data for recent years in which all those living with diagnosed HIV are reported through ongoing monitoring, for example of CD4⁺ or viral loads.

Approaches to estimating the total PLHIV include back-calculation models to estimate HIV incidence and time from infection to diagnosis, prevalence surveys, multiparameter evidence synthesis and use of Spectrum software [32]. Back-calculation or other modelling approaches incorporating routinely collected HIV surveillance data may be most suitable for the concentrated HIV epidemics in Europe [30,32–38]. ECDC has developed a modelling tool [29] to support countries in generating robust estimates for PLHIV by using HIV surveillance data.

However, many countries in the European region lack HIV surveillance data for earlier years of the epidemic, or their data suffer from substantial under-reporting. In such cases, it is impossible to derive the number ever diagnosed directly from surveillance data and, therefore, challenging to produce robust estimates of PLHIV. Methods are being developed to capitalize on available years of data, for

Table 1. Summary of recommendations for monitoring a four-stage HIV continuum of care in Europe in a given year (YYYY).

Stage	Definition	Numerator	Denominator	Notes
(1) Number of PLHIV ^a	Total number of PLHIV in the country by the end of the given year YYYY	Estimated number of PLHIV, diagnosed and undiagnosed, including those who in-migrated and excluding those who out-migrated or died by the end of the given year YYYY	N/A	A back-calculation modelling approach using routine HIV surveillance data, e.g. ECDC HIV Modelling Tool [29], is recommended. Challenges may include accounting for in-migration (e.g. separating out infections that occurred after arrival into the country) or out-migration, and incomplete surveillance data to feed models. Availability of CD4 ⁺ cell counts and HIV stage at diagnosis to estimate the undiagnosed fraction may also present a challenge [30,31]
(2) Diagnosed	Number diagnosed with HIV. Expressed as a number and proportion of PLHIV (see denominator definition)	Number ever diagnosed with HIV by the end of the given year YYYY, including those who in-migrated and excluding those who out-migrated or died by the end of the year YYYY	Total number of PLHIV (as defined for stage 1)	Ideally, the number diagnosed should not be restricted to those in care. Where it is not possible to include all diagnoses since the beginning of the epidemic (e.g. due to limited years of surveillance), the diagnosed population may be estimated, e.g. using modelling, or triangulating with other data sources e.g. health insurance data. Mortality and migration should be estimated where these data are unavailable and linkage to migration/death records is not feasible
(3) On ART	Number who are taking ART in the given year YYYY. Expressed as a number, as a proportion of those diagnosed, and as a proportion of all PLHIV (see denominator definitions)	Number with at least one record of ART (prescribed or, ideally, dispensed) in the year YYYY, regardless of treatment eligibility criteria. Those who in-migrated by end of YYYY are included and those who out-migrated or died by end of YYYY are excluded. ART is defined as any ART regimen since diagnosis, regardless of the number of antiretroviral drugs	(A) Number diagnosed with HIV (as defined for stage 2), regardless of treatment eligibility criteria (B) Total number of PLHIV (as defined for stage 1)	Denominator A, the number diagnosed, should exclude those who died or out-migrated by the end of the year YYYY. Ideally the same data source is used as for stage 2. Preexposure prophylaxis regimens are not included in the numerator for 'on ART'. Those with missing ART information are assumed to be untreated
(4) Virally suppressed	Number virally suppressed with <200 copies/ml. Expressed as a number, as a proportion of those on ART, and as a proportion of all PLHIV (see denominator definitions)	Number on ART whose most recent HIV RNA measurement in the given year YYYY was <200 copies/ml, or below the level of detection of the assay. Those who in-migrated by end of YYYY are included and those who out-migrated or died by end of YYYY are excluded	(A) Number on ART (as defined for stage 3) (B) Total number of PLHIV (as defined for stage 1)	Ideally the same data source is used as for stages 2 and 3. Those with missing viral load measurements in the year YYYY are assumed to be unsuppressed

ART, antiretroviral therapy; ECDC, European Centre for Disease Prevention and Control; PLHIV, people living with HIV; RNA, ribonucleic acid; YYYY, denotes the given year of interest for reporting the continuum.

^aCountries should aim to provide this and all subsequent stages disaggregated by key population subgroups.

example by using CD4⁺ data [39] or through statistical modelling to reconstruct data for earlier years [40]. Triangulation with other data sources, such as national clinic-based surveys to estimate the number diagnosed and in care/not in care [37], or using health insurance data [41], may offer alternative solutions. As in the United States [7,16], European countries also encounter difficulties accounting for migration and deaths, which are often incompletely captured through surveillance data, particularly non-AIDS-related deaths. Although longer term solutions are clearly required, for example enhancing surveillance systems to enable linkage to national migration and death records via unique identifiers [42], in the short-term, deaths and out-migrations should at least be estimated and excluded from each stage. Efforts to account for in-migration, distinguishing new HIV infections after arrival in the country, are also warranted [43].

Regarding the number 'on ART', we suggest that all patients who received or were prescribed ART at least once during the year of interest are included. This has been recommended by the International Association of Providers of AIDS Care (IAPAC) [18] and aligns with the WHO indicator 'currently on ART' [28]. Although ART initiation is most commonly used to measure 'on ART', recent follow-up records for those continuing on ART are also available in many European countries and other regions [8,12,44,45]. For consistency in global and regional reporting, and given that individuals not yet eligible for ART can potentially transmit HIV, it is important that the proportion on ART is not restricted to those eligible for ART based on prevailing treatment guidelines [14,28]. Rather, differences in guidelines, together with epidemic contexts, should be considered when interpreting and comparing national continua [14], or evaluating ART programme performance within countries [28]. However, treatment guidelines will become less important in explaining differences in the proportions on ART, as European and global guidelines converge on immediate ART initiation [46,47].

For the final stage, we recommend using a cross-sectional 'snapshot' of viral loads at a particular time point [28], for example the latest viral loads recorded in the year of interest [18]. Although this single measure may overestimate suppression by discounting time spent above the threshold during the year [18,21,48], it is transparent and easy to communicate to policy makers. It is also easier to standardize and measure, particularly for countries lacking cohort data, than other longitudinal measures of interest [14,28,34,44] that require further development. To allow for changes over time in the lower detection limits of viral loads assays, we recommend using a viral load threshold of less than 200 copies/ml. A threshold of 200 copies/ml for population-level monitoring is consistent with recommendations from a recent systematic review [7], guidelines produced by IAPAC [18] and the US Centers for

Disease Control and Prevention [23] and recent data published on transmission potential [49]. Although the WHO-suggested threshold of 1000 copies/ml may be more suitable at a global level [28], less than 200 copies/ml is considered appropriate for European countries.

Initiatives to improve monitoring of the care continuum

Attempts to construct national-level continua have often revealed gaps in data availability. Data for downstream stages, particularly viral suppression, are often only available through clinical cohorts and less frequently reported than the number diagnosed [12,20], which may be derived from publicly available surveillance data. Collaboration between those responsible for case surveillance and cohorts may facilitate construction of complete national-level continua [17,50]. Use of cohorts for multiple stages can improve the internal consistency of estimates [51], if representativeness is rigorously assessed and data are appropriately weighted to overcome potential biases and allow generalizability of findings [52]. European countries should also be encouraged to establish patient monitoring systems in all facilities that care for HIV patients [28].

Initiatives are needed to disaggregate HIV continua by populations of interest to target testing and treatment programmes appropriately. Few such continua have been published in Europe [41,53]. A key challenge relates to missing data for transmission group, as they are not collected, sometimes owing to legal restrictions, recorded or disclosed. Population-based bio-behavioural surveys, incorporating the collection and measurement of biological markers of HIV infection and treatment may capture the whole universe of a particular subgroup through carefully designed recruitment approaches [54]. For many European countries, modelling approaches using routine surveillance data, in which transmission group is collected and, if appropriate, missing information is imputed, may be a more feasible alternative [41].

Conclusion

In summary, we recommend that European countries monitor a standardized four-stage HIV continuum of care that aligns with the UNAIDS 90–90–90 framework. Our recommendations are based on expert opinion [22] and evidence from published literature and may apply to other countries beyond Europe. Additional stages of the continuum remain important as they may provide insights related to the quality of care and programme performance. Further guidance on

standardization of definitions, support to countries, for example in estimating the total number of PLHIV, and investments in data collection and measurement [28,42], for example establishing pseudo-cohorts or linking to death/migration records, are needed urgently if we are to have faith in our estimates as we progress towards, reach and surpass the 90–90–90 target in Europe.

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Conflicts of interest

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