Author's response to reviews

Title: Good continuum of HIV care in Belgium despite weaknesses in retention and linkage to care among migrants

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Author's response to reviews: see over
Dear editor, dear reviewers,

We thank you for the comments on the manuscript entitled “Good continuum of HIV care in Belgium despite weaknesses in retention and linkage to care among migrants”. We have revised the manuscript as per your suggestion, addressing the comments of the reviewers, who raised some important issues that helped us to reflect on the subject of the HIV care continuum and to improve the content of the paper.

Following the reviewers’ comments we have revised the method for combining the estimates obtained for each stage of the continuum into the overall cascade of HIV care. Results and discussion have been adapted in consequence.

The text was revised for the quality of the written English.

**Answers to reviewer Janne Estill**

- **Major compulsory revisions**

2) My main concerns in the methodology are the definitions of the rates and proportions used in the cascade. Since proportions from the different steps are combined into overall estimates of virally suppressed among all diagnosed patients, the authors should be careful to check that these proportions are combinable.

The reviewer rightly points out the challenge to depict the most accurately the situation of the PLHIV along the continuum of HIV care based on the routine HIV surveillance data available. Various methods for analysing the HIV care continuum have been used in other publications.

Following this concern expressed by the reviewer, we have adapted our method for combining the proportions found in each stage to an overall cascade in order to describe better the distribution of the diagnosed HIV population living in Belgium between each stages of the continuum of HIV care in 2011.

In the revised method, estimates of the diagnosed populations not linked and not retained in HIV care living in Belgium were calculated by projecting proportions of late entry in care and re-entry found in the previous years instead of using nationalities to classify patients as in or out of the country as previously done.

The updated method is described in the text:

p. 5, line 161: “Continuum of HIV care. Proportions estimated for each stage of the continuum of HIV care were combined to obtain the distribution of the diagnosed HIV individuals living in Belgium in 2011 by stage of the continuum.”
The total diagnosed HIV population living in Belgium was obtained by summing the estimated population retained in care in 2011 with the estimated number of HIV-positive persons diagnosed but not linked to care in 2011 and the estimated number of persons previously in HIV care but not retained in care in 2011. Using the data of 2007, we first estimated the proportion of patients that entered in care later than one year after diagnosis. We then applied this proportion of late entry in care to patients diagnosed in the years following 2007 to obtain an estimate of the total number of patients entering late in care. From this total we subtracted those entered in care before the end of 2011 in order to obtain the estimated number of diagnosed patients not linked to care and expected to enter in care after 2011. Next we estimated for the patients in care in 2007 and not retained in care after one year, the proportion who re-entered care later. Using a similar computation, the number of patients entering back in care was calculated for the years following 2007. From the cumulative total, we subtracted patients already re-entered in care by end of 2011 in order to obtain the estimated number of patients not retained in care and expected to re-enter in care after 2011. Patients estimated to never enter or re-enter care were considered as having left the country. We also hypothesised that persons diagnosed before 2007 were not expected to enter in care after 2011. The next stages of the continuum of HIV care were estimated by applying the proportions of patients on ART and with VL suppression to the population retained in HIV care."

The updated results of the overall continuum of HIV care are presented in the results section and Figure 2 has been modified accordingly.

In addition to the results below, we provide in attachment a document (Estimates of populations in HIV care.doc) with the detailed calculations for the estimates of the population expected to enter in care after 2011 and of the population expected to re-enter in care after 2011.

p. 8, line 243: “Proportions of diagnosed patients along the continuum of HIV care in Belgium. We estimated that 11478 patients were retained in HIV care in 2011 by applying the proportion of retention in HIV care of 92.2% observed in 2010 to the 12449 HIV+ patients with at least one laboratory record in 2011. The proportion of late entry in care of 4.7% observed in the 2007 data was applied to the persons diagnosed in the years following 2007. After subtraction of those already entered in care, we found that 221 patients were expected to enter in care after 2011. Re-entry in care among patients not retained in care for one year after 2007 was estimated at 39.5%. By applying this proportion of re-entry to the patients not retained in care in the following years and then subtracting those already re-entered in care, we estimated that 940 persons were expected to re-enter in care after 2011. After combining these results, the population of diagnosed HIV patients living in Belgium at the end of 2011 (n=12639) was distributed as follows: 11 478 patients (90.8%) were estimated to be retained in HIV care, 221 (1.8%) were not linked to HIV care and 940 (7.4%) were not retained in HIV care. The estimated proportions of 84.6% of patients in care on ART and 83.4% of patients with viral suppression were applied to the population retained in HIV care. We obtained the estimates of 76.8% of the diagnosed HIV population living in Belgium on ART and 64.1% with suppressed VL.”
Assumptions made in the revised method have been underlined in the discussion section.

p. 14, line 392: “We used the data of 2007 to estimate the proportions of late entry and re-entry into HIV care because time of follow-up for these patients was at least 4 years. We assumed that these proportions did not change over the next years and applied them to estimate the number of patients with late entry and with re-entry during the following years. However as linkage to care within one year improved slightly after 2007, the number of patients expected to enter late in HIV care based on the results of 2007 and hence the population of persons diagnosed and not linked to HIV care living in Belgium might be slightly overestimated.”

2a) Linkage to care is now defined as a proportion of all patients diagnosed between 2007 and 2010 who are linked until 2011. This may not be appropriate since those who were diagnosed in 2007 have a much longer follow-up time than those who were only diagnosed in 2010. Is the intention to calculate the proportion of patients who ever will be linked to care (which would be expected to be very high since most patients would seek care at the latest when they develop symptoms), or who are linked to care within a certain time period? I expect that the outcome that is used now will provide an estimate which is between these two values.

Figure 1 shows that most patients (98%) were retained in care within 1 year of diagnosis. Is this true also for those patients with a long follow-up time? If yes, this would justify the method the authors have used for calculating the proportions of linked patients.

We have adapted the definition of linkage to HIV care to include a period of linkage to care within 1 year of HIV diagnosis.

p. 5, line 152: “Linkage was defined as having at least one VL or CD4 count recorded within 1 year of HIV diagnosis, with a window of 7 days for VL records to prevent incorrectly counting VL measurements performed at the time of diagnosis as initial HIV care visit.”

And results have been adapted to the adapted definition:

p. 7, line 205: “Among newly diagnosed individuals, 87.0% patients entered in care within one year of diagnosis. This proportion increased over the years (2007: 84.5%, 2008: 87.4%, 2009: 87.0%, 2010: 89.0%; p<0.001).”

Results presented in Table 2 were adapted using the updated definition, observed associations were not modified by the modification in the definition of linkage to HIV care.

2b) Also the definition of retention should be still clarified. What does "in care in 2010" - is one lab measurement in 2010 sufficient?

The definition has been clarified in the text as follows:

p. 5, line 155: “Retention in care was defined as the proportion of patients in care in 2010, those having one CD4 or VL measure during that year, who had at least one record of CD4 or VL in 2011.”

To be in line with the revised method for the overall estimate of the continuum of HIV care among the patients in HIV care living in Belgium in 2011, we re-estimated the proportions on ART and of VL
suppression on all the patients in care in the ARCs instead of only on those retained in care from 2010 as in the previous version. We indicated it in the definition as follows:
p.5, line 160: “ART was defined as a record of ART prescription at the end of the year 2011.
Proportions of patients on ART and with suppressed VL were measured among patients in care in the ARCs in 2011. Suppressed VL was defined as the last measured VL<50 copies/mL.”

Results and table 3 were adapted accordingly. Associations found were not different except low CD4 which was not significantly associated with VL suppression anymore but remained associated with ART uptake and SSA nationality that was associated with less VL suppression in the multivariate analysis. These findings were added in the result and discussion sections as follows:

p. 8, line 233: “In univariate analyses... Patients diagnosed for clinical reasons and with lower CD4 count at first contact had higher ART uptake. Sub-Saharan African patients on ART had less VL suppression (Table 3).
In the multivariate analyses, younger age remained associated with lower ART uptake and less VL suppression. HIV testing requested for clinical reasons and lower CD4 count at first contact remained associated with higher ART uptake and Sub-Saharan African nationality with less VL suppression.”

p. 11, line 309: “None of the socio-demographic factors studied impacted ART uptake and VL suppression, except the SSA nationality that was associated with lower VL suppression, although the difference with Belgians was small. These results suggests that ARV treatment needs are equally covered for all patients having access to regular HIV care. Suboptimal ART adherence potentially related to socio-economic factors (18) might explain the slightly lower VL suppression among SSA.”

1) It is unclear what has happened to the patients dropping out in the different stages of the cascade. For example, is there any way to roughly estimate the proportion of different reasons for not being retained in care (e.g. deaths, stopping treatment, moving out of the country, etc.)? How about the reasons of not being virally suppressed?
With the revised method, the population diagnosed with HIV living in Belgium is more clearly classified as being diagnosed and in care, being diagnosed and not entered in HIV care and being diagnosed, having entered in HIV care but not retained in HIV care.
We have no information on the outcomes of the patients that have left the country before linkage to HIV care or after not being retained in HIV care. We have specified this in the discussion.

p. 13, line 387: “There are some limitations in this study. These results do not inform on the outcomes of the patients after they have left the country.”

With the revised method, deceased patients are not included in the denominator population of diagnosed HIV individuals living in Belgium. No information is available on those deceased after not being linked to HIV care or not re-entering in HIV care, although we do believe that a large majority of those dying in Belgium are captured by the data collection, and have at least one lab record. In the future we plan to link our data on LFU with the national registry of death to complete our information on death.
We have not collected data on reasons for non VL suppression, and were therefore not able to describe why patients were not virally suppressed. Although we hypothesized that for SSA migrants non VL suppression might be related to suboptimal adherence. This was added in the text:

p. 11, line 312: “Suboptimal ART adherence potentially related to socio-economic factors (18) might explain the slightly lower VL suppression among SSA. Other reasons for non VL suppression might be ARV resistance or recent ART initiation at the time of VL measure but this information was not collected.”

3) It would be helpful to present the guidelines of HIV care that are applied in Belgium. Is ART recommended for all HIV diagnosed patients, regardless of CD4 cell count, clinical stage, partnerships, etc? If not, how often is the ART eligibility monitored? What is the schedule of recommended laboratory tests (VL, CD4, etc) before and during ART?
Information on HIV care guidelines have been added in the introduction:
p. 3, line 107: “Access to HIV care services in Belgium is, in principle, ensured to all HIV-infected individuals through the compulsory national health insurance. Antiretroviral therapy is reimbursed when patient’s CD4 count is below or equal to 500 cells/mm³ or below 25% and also in case of clinical symptoms. There is no national guideline for HIV care, clinicians follow the guidelines of the European AIDS Clinical Society for clinical and laboratory monitoring (9).”

4) A brief description of the Belgian health care system from the point of view of HIV would also be helpful. What are the different routes of testing, i.e. where can an individual get tested if he/she suspects being infected? Are there any campaigns or other active screening interventions in place among risk populations (MSM, IDUs, FSW, migrants from high-prevalence countries)? How is it ensured that e.g. illegal immigrants and IDUs can get tested without the fear of having legal consequences – do the authors expect a bias in such patient groups?
A description of the HIV testing services and outreach programmes was added. There is no legal consequence of HIV seropositivity in Belgium, neither for IDUs, neither for illegal immigrants.

p. 3 line 98: “Services for HIV testing in Belgium are available either in primary care, secondary care (specialized clinics-outpatient), hospitals and decentralized projects. Three Aids Reference Centers (ARC) are funded to perform low threshold testing and to offer free anonymous testing. Outreach programs are set up to better target specific groups at increased risk for HIV. These programs are organized by the ARCs themselves or through a collaborative effort with NGOs working with the specific target population. Compared to other European countries (29), Belgium has a high and relatively stable rate of HIV testing. In 2013, a total number of 695.433 HIV tests were performed, with a testing rate of 62 per 1000 inhabitants.”

- Minor essential revisions:
5) Typo in the last paragraph of Results: the upper proportion of virally suppressed should be 72%, not 86%.
Results were adapted with the estimations from the revised method.
Discretionary revisions

6) The UNAIDS has recently published the ‘90-90-90’ targets. This could be also discussed in this study. According to the targets, by 2020 81% of patients diagnosed with HIV should be virally suppressed. This analysis shows that there is still work to do to achieve these targets even in high-income countries such as Belgium.

We followed this proposal and a paragraph on the UNAIDS targets was added in the discussion.

p. 12, line 342: “The UNAIDS has recently published global targets of 90% of PLHIV knowing their status, 90% of those receiving ART and 90% of those having suppressed VL by 2020 (27). The results presented here show that today Belgium is not yet fulfilling these targets. With the recent release of the results of the START study supporting added benefit of offering treatment to everyone with HIV (28) however, we may expect an increase in the proportion of patients on ART in the coming years. This might also increase the retention in HIV care among recently diagnosed patients, who will initiate ART immediately, as ART uptake was associated with higher retention in HIV care. Efforts should then concentrate on the diagnosis of persons unaware of their HIV infection in order to initiate their treatment earlier.”

Answers to reviewer David Burns

• Minor Essential Revisions

1. P7, line 223: “…between 62 and 86% of those diagnosed with HIV…” appears incorrect. Did you mean “between 62 and 72%”? Estimates were obtained from the revised method and this paragraph was rewritten.

2. P8, line 234: Please clarify what is meant by “This is supplemented by collaborations with prevention and testing associations that contributes to the low attrition along the care continuum.” If the benefit of these collaborations is limited to their contribution to linkage to care, then it would be preferable to state it in that manner.

We have specified the benefit of these collaborations more clearly in the text.

p. 9, line 268: “In addition, those specialized structures have developed collaborations with prevention and testing associations that contribute to a more efficient linkage to HIV care.”

3. P10 and following: The authors note that “attrition in the early stages of linkage and retention” and undiagnosed persons are likely to be contributing disproportionately to onward transmission. If there are efforts in place (or in planning) to further identify these populations so they can be targeted more effectively for HIV prevention, testing, and care (eg, combined phylogenetic and epidemiologic analyses that characterize individuals in acute transmission clusters), it would be helpful to include these options in this discussion.
We are planning a project aiming at estimating and characterizing undiagnosed people living with HIV in Belgium through modelling of our routine HIV surveillance data. This project should permit to better target HIV testing towards populations with the highest rate of undiagnosed infections.

This information was added in the text as follows:

p.13, line 375: “A project aiming at estimating and characterizing the undiagnosed HIV-infected populations by mathematical modelling of routine HIV surveillance data will be conducted in the coming years. Its results will be used to target HIV testing to groups that require it most.”

We are not aware of any project of combination of phylogenetic and epidemiological data to identify clusters resulting from recent transmissions and to actively trace other contact persons (peers in the network) of the clustered individuals currently in Belgium.

4. P12, line 336 and following: Would move these data to the results section.
The estimate of the undiagnosed population living with HIV is based on a triangulation of existing information from different sources: small-scale surveys, other surveillance and other countries’ results, that gives a rough estimate. Whilst the results section show only results of the analysis of the Belgian national data. We would prefer to keep the rough estimate of undiagnosed in the discussion section to differentiate clearly what is the results of our analysis and what comes from background information.

- Discretionary Revisions
1. P2, Abstract, Results: The most important summary statement is that among all persons diagnosed with HIV, 62% had an undetectable viral load. Eg, “…of whom 86% had an undetectable viral load (<50 copies/ml). Among all persons diagnosed with HIV, an estimated 62% were virally suppressed.”
The abstract was updated with the results of the revised method, including the estimation of VL suppression in the results section.
p. 2: “Of all diagnosed HIV patients living in Belgium in 2011, an estimated 98.2% were linked to HIV care, 90.8% were retained in care, 76.8% were receiving antiretroviral therapy and 64.1% had an undetectable viral load (<50 copies/ml).”

2. P9, line 263: A valuable suggestion that might be worth expanding on. Is it possible to estimate to which countries HIV+ persons are most likely to emigrate? Ideally, this could lead to better coordination of continuity of care with countries as far away as Africa, particularly with those that may have important economic and cultural links with Belgium.
We do not have data on countries of emigration. We do know that more than half of the Sub-Saharan African diagnosed with HIV in Belgium originate from 4 countries: Cameroun, DR Congo, Guinea and Rwanda. But no data has been collected on whether emigrants will go back to their original country after emigration for Belgium or go to a country bordering Belgium. We do find your suggestion very interesting and we will enquire how in the future we could get a better understanding of the emigration trajectory of these HIV+ persons.
3. P9, line 269: Another valuable suggestion. If there are resources in place that enable following such cases up and offering partner services, it would be worth noting.

Improving skills of the physicians in communication on sexual health and in HIV screening through improved training is one of the recommendations of the first Belgian national HIV plan that was launched in 2013. This information was added in the text:

p.10, line 304: “... facilitated by training of caregivers on sexual health counselling and HIV screening. These interventions are part of the recommendations of the Belgian National HIV plan that has been launched in 2013 (22).”

Thank you for considering this revision.

Yours sincerely,

Dominique Van Beckhoven