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The high proportion of late HIV diagnoses in the USA is likely to stay: findings from a mathematical model

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A static model of undiagnosed and diagnosed HIV infections by year of infection and year of diagnosis was constructed to examine the impact of changes in HIV case-finding and HIV incidence on the proportion of late diagnoses. With no changes in HIV case-finding or incidence, the proportion of late diagnoses in the USA would remain stable at the 2010 level, 32.0%; with a 10% increase in HIV case-finding and no changes in HIV incidence, the estimated proportion of late diagnoses would steadily decrease to 28.1% in 2019; with a 5% annual increase in HIV incidence and no changes in case-finding, the proportion would decrease to 25.2% in 2019; with a 5% annual decrease in HIV incidence and no change in case-finding, the proportion would steadily increase to 33.2% in 2019; with a 10% increase in HIV case-finding, accompanied by a 5% annual decrease in HIV incidence, the proportion would decrease from 32.0% to 30.3% in 2011, and then steadily increase to 35.2% in 2019. In all five scenarios, the proportion of late diagnoses would remain stable after 2019. The stability of the proportion is explained by the definition of the measure itself, as both the numerator and denominator are affected by HIV case-finding making the measure less sensitive. For this reason, we should cautiously interpret the proportion of late diagnoses as a marker of the success or failure of expanding HIV testing programs.

Keywords: HIV; diagnosis; mathematical model; surveillance; USA

Late diagnosis of HIV is associated with increased morbidity, mortality, and health-care costs (Girardi, Sabin, & Monforte, 2007; Paltiel et al., 2006). Many countries advocate routine HIV testing as a means to increase timely diagnosis and reduce late diagnoses (Branson et al., 2006; Delpierre, Cuzin, & Lert, 2007; Hamill et al., 2007). However, despite testing campaigns that have increased testing among high-risk and general populations (Myers et al., 2012; Xia et al., 2006), late diagnosis, defined as AIDS diagnosis within 12 months of an HIV diagnosis, remains common. The proportion of late diagnoses has not only been high, e.g., 32% in the USA and 15–38% in Europe but also stable and, in some places, increasing (Adler, Mounier-Jack, & Coker, 2009; Centers for Disease Control and Prevention [CDC], 2009; Delpierre, Dray-Spira, et al., 2007; Lesko, Cole, Zinski, Poole, & Mugavero, 2013; Tang, Levy, & Hernandez, 2011; Yang et al., 2010).

Does a high, stable proportion of late diagnoses mean that efforts to expand HIV testing have not reduced the number of persons who are long-term unaware of their HIV infection (BBC News, 2005)? We hypothesize that a high and stable proportion of late diagnoses might reflect the limitations of the measure itself, as expanded HIV testing initiatives can affect both the numerator and the denominator of this measure in such a way as to keep the proportion relatively stable even as more persons are diagnosed at different stages of HIV infection. In this paper, we use a mathematical model to demonstrate the impact of changes in HIV case-finding and incidence on the proportion of late diagnoses.

Methods

Study design

A static model of undiagnosed and diagnosed HIV infections by year of infection and year of diagnosis was constructed using Microsoft Excel (Figure 1). Table 1 shows the input data and sources for parameters (CDC, 2009; Kuo, Taylor, & Detels, 1991; Prejean et al., 2011; Ramaswamy et al., 2012). We assumed an annual death rate of 0.2% among undiagnosed persons. The overall case detection rate among persons in the second to ninth year of infection was calculated based on the first and tenth year case detection rates and the proportion of late diagnoses. With a fixed overall rate, variable rates by year of infection have no impact on the number of patients undiagnosed entering their tenth year of infection and the estimate of the proportion of late diagnoses. Therefore, for easy modeling, we assumed an equal case detection rate among persons in the second to ninth year of infection.

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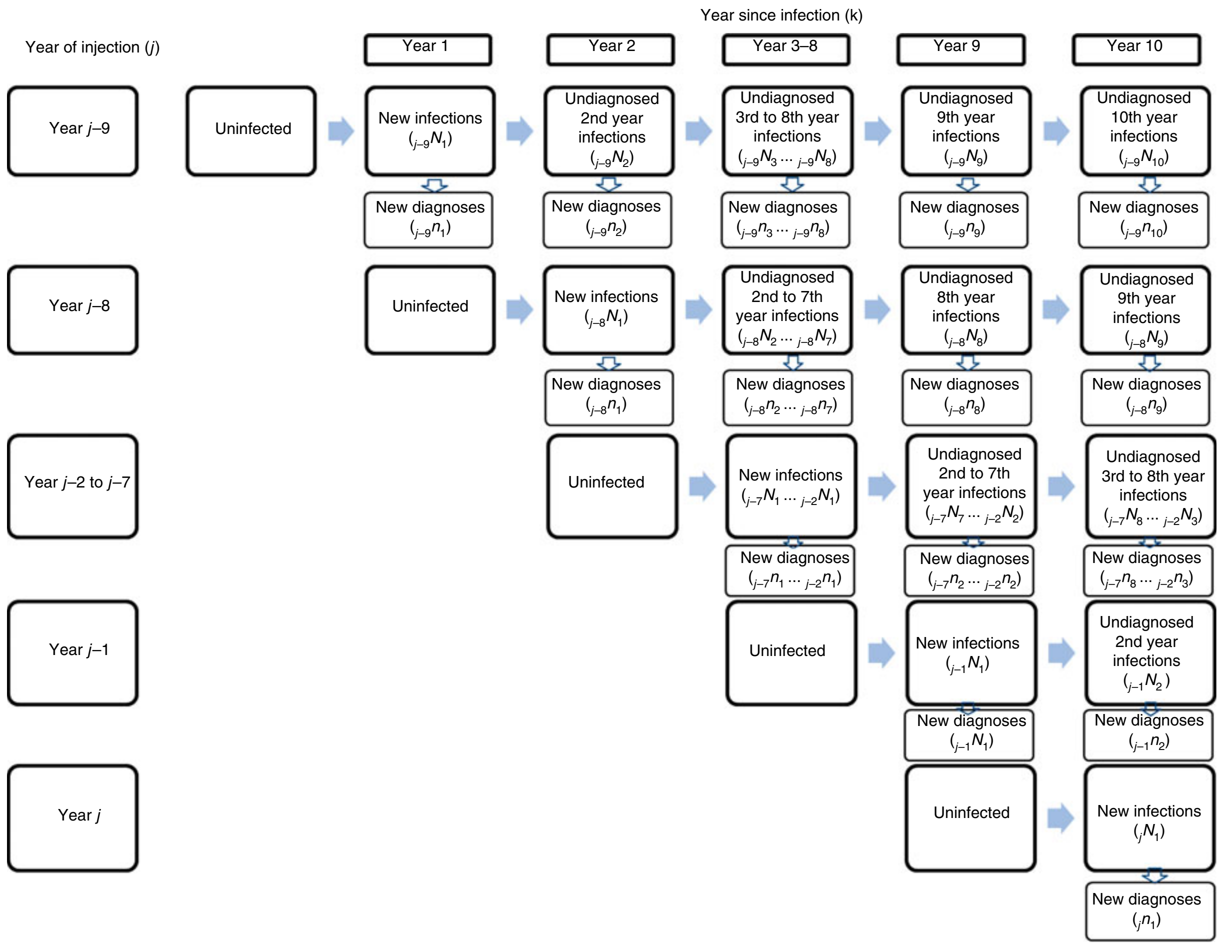

Figure 1. A static model of undiagnosed and diagnosed HIV infections, by year of infection (row) and years since infection (column).

In Figure 1, the row shows when (Year *j*) patients were infected; *j* can be any natural number equal to or greater than 1. The column shows how long (*k*th year of infection) patients have been infected; *k* is a natural number between 1 and 10. To make it easier to present and understand, we synchronized the column (*k*th year of infection) year with calendar year by making all patients acquired HIV infection on 1 January. In the first calendar year after they acquired HIV infection, all patients were in their first year of infection; in the next calendar year, all patients were in their second year of infection, and so on. In the tenth calendar year after they acquired HIV infection, all patients were in their tenth year of infection, and those who remained undiagnosed at the beginning of the year would develop AIDS and be diagnosed by the end of the tenth calendar year/tenth year of infection.

$_jN_k$ represents the number of patients who acquired HIV infection in Year *j* and remained undiagnosed at the beginning of the *k*th calendar year as *k*th year of infection; $_jn_k$ represents the number of patients diagnosed in the *k*th year. $_jN_1$ is a special case that is the number of new infections in Year *j*, and in other situations the number of undiagnosed ($_jN_k$) is the number of undiagnosed infections on 1 January of the previous year minus the number of patients later diagnosed in the previous year (Equation 1).

$$_jN_k = {}_jN_{k-1} - {}_jn_{k-1}\ (j \in N_1;\ k \in \{2, \ldots, 10\}) \quad (1)$$

For simplicity, infections acquired prior to Year *j*–9 are not shown in Figure 1, so only the column Year 10 shows the full picture of undiagnosed and diagnosed HIV infections. Undiagnosed HIV infections ($_jN$) include persons who newly acquired HIV infection in Year *j* ($_jN_1$) and persons who acquired HIV infection in previous years (Year *j*–9 through Year *j*–1), were in their second to tenth year of infection, and had not been diagnosed at the beginning of the tenth calendar year (Equation 2). New diagnoses ($_jn$) include persons who were diagnosed in the same year (Year *j*) as they were infected and persons in their second to tenth year of infection (Equation 3).

$$_jN = {}_jN_1 + {}_{j-1}N_2 + {}_{j-2}N_3 + {}_{j-3}N_4 + {}_{j-4}N_5 + {}_{j-5}N_6 + {}_{j-6}N_7 + {}_{j-7}N_8 + {}_{j-8}N_9 + {}_{j-9}N_{10} \quad (2)$$

Table 1. Input data for the model and sources.

Variable	Value	Source
Annual HIV incidence in the last 10 years	48,000	Prejean et al. (2011)
Average annual increase in case detection rate in the last 10 years	0.5%	Assumption
Death rate among undiagnosed persons	0.2%	Ramaswamy et al. (2012)
Time to develop AIDS after infection, if undiagnosed	10 years	Kuo et al. (1991)
Proportion of late diagnoses	32%	CDC (2009)
Case detection rate in the first year of infection	25%	Assumption
Case detection rate in the second to ninth year of infection	10.07%	Calculated based on 25% case detection rate in the first year and 100% in the tenth year, 32% proportion of late diagnoses, and an assumption of equal case detection rate in the second to ninth year
Case detection rate in the tenth year of infection	100%	Assumption

AIDS, acquired immunodeficiency syndrome; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; NYC DOHMH, New York City Department of Health and Mental Hygiene.

$$_jn = {_jn_1} + {_{j-1}n_2} + {_{j-2}n_3} + {_{j-3}n_4} + {_{j-4}n_5} + {_{j-5}n_6} + {_{j-6}n_7} + {_{j-7}n_8} + {_{j-8}n_9} + {_{j-9}n_{10}} \quad (3)$$

We used the case detection rate (R) to measure HIV case-finding, which is the number of newly diagnosed cases in a given year (n) divided by the number of undiagnosed HIV infections at the beginning of the year (N), including patients who remained undiagnosed at the beginning of the year and persons who newly acquired HIV infection on 1 January. Equation 4 shows the overall case detection rate in Year j; Equation 5 is the rate among new infections; Equation 6 gives the case detection rate among persons in their second to ninth year of infection; and Equation 7 shows that the case detection rate among persons in their tenth year of infection.

$$_jR = \frac{_jn}{_jN} \quad (4)$$

$$_jR_1 = \frac{_jn_1}{_jN_1} \quad (5)$$

$$_jR_{2-9} = \frac{_{j-1}n_2}{_{j-1}N_2} = \frac{_{j-2}n_3}{_{j-2}N_3} = \frac{_{j-3}n_4}{_{j-3}N_4} = \frac{_{j-4}n_5}{_{j-4}N_5} = \frac{_{j-5}n_6}{_{j-5}N_6} = \frac{_{j-6}n_7}{_{j-6}N_7} = \frac{_{j-7}n_8}{_{j-7}N_8} = \frac{_{j-8}n_9}{_{j-8}N_9} \quad (6)$$

$$_jR = \frac{_{j-9}n_{10}}{_{j-9}N_{10}} = 100\% \quad (7)$$

In Equation 8, $_jP$ denotes the proportion of late HIV diagnoses, which is the number of late diagnoses ($_{j-9}n_{10}$) divided by the number of all new diagnoses ($_jn$). With a 100% case detection rate among patients in their tenth year of infection, improvement in HIV case-finding would have no effect on the numerator this year but would reduce the number of late diagnoses in the following years. Changes in HIV incidence also have no effect on the numerator this year, because newly infected persons who are diagnosed in the year of infection are early diagnoses and will only be included in the denominator. An increase in the overall case detection rate can drive the proportion of late diagnoses down by increasing the denominator (total number of new diagnoses); a decrease in HIV incidence can drive the proportion up by decreasing the denominator with a smaller $_jn_1$, the number of diagnosed new infections.

$$_jP = \frac{_{j-9}n_{10}}{_jn} = \frac{_{j-9}n_{10}}{_jn_1 + {_{j-1}n_2} + {_{j-2}n_3} + {_{j-3}n_4} + {_{j-4}n_5} + {_{j-5}n_6} + {_{j-6}n_7} + {_{j-7}n_8} + {_{j-8}n_9} + {_{j-9}n_{10}}} \quad (8)$$

Study population

This modeling of proportion of late diagnoses does not depend on the size of undiagnosed HIV population but the distribution of duration of infection. To measure the impact of changes in HIV case-finding and HIV incidence on the proportion of late diagnoses, we constructed a model of an undiagnosed HIV population in the USA (Prejean et al., 2011). We examined the impact of changes in HIV case-finding and HIV incidence on the

Table 2. Estimated number of undiagnosed and diagnosed HIV infections in the USA in 2010 by duration of infection based on a mathematical model.

Duration of infection (years)	Total ($A + B$)	Diagnosed (A)	Undiagnosed (B)	Case detection rate (%) $A/(A + B)$
1	48,000	12,000	36,000	25.00
2	35,987	3624	32,363	10.07
3	32,352	3258	29,094	10.07
4	29,084	2929	26,155	10.07
5	26,145	2633	23,512	10.07
6	23,503	2367	21,136	10.07
7	21,128	2128	19,000	10.07
8	18,993	1913	17,080	10.07
9	17,073	1719	15,354	10.07
10	15,347	15,347	0	100.00
Total	267,612	47,916	219,696	17.91

proportion of late HIV diagnoses in the next 30 years in five scenarios: (1) no changes in HIV case-finding or incidence; (2) no changes in HIV case-finding, but an increasing trend in HIV incidence; (3) no changes in HIV case-finding, but a decreasing trend in HIV incidence; (4) an increase in HIV case-finding, but no changes in HIV incidence; and (5) an increase in HIV case-finding with a decreasing trend in HIV incidence.

Sensitivity analysis

We conducted sensitivity analyzes to determine how the model results are impacted by each parameter individually with an improvement ranging from 10% to 30% in HIV case-finding and from 20% annual decrease to 5% annual increase in HIV incidence.

Results

Number of undiagnosed and diagnosed HIV infections

Based on the model, there were 267,612 undiagnosed HIV infections in the USA in 2010 (Year 0) with 48,000 new infections and 219,612 undiagnosed prevalent cases, of whom 35,987, 32,352, 29,084, 26,145, 23,503, 21,128, 18,993, 17,073, and 15,347 were in their second to tenth year of infection, respectively (Table 2). A total of 47,916 cases were diagnosed in 2010 including 12,000 new infections, 20,569 in their second to ninth year, and 15,347 in their last/tenth year of infection.

Trends in proportion of late diagnoses

Figure 2 shows the trends in proportion of late diagnoses in five scenarios. A stable trend from 32.0% to 31.8% in

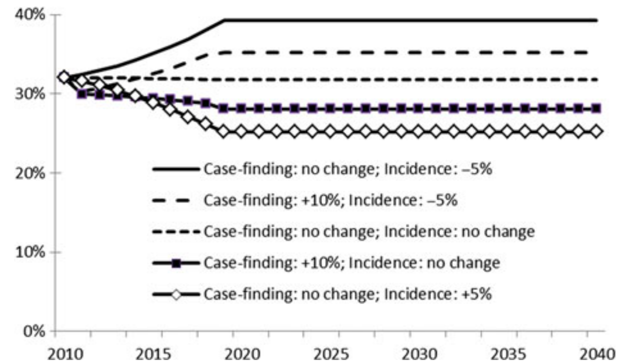

Figure 2. Trends in the proportion of late HIV diagnoses in five scenarios in the USA, 2010–2040, based on a mathematical model.

the proportion of late diagnoses would be observed in the next 30 years when there are no changes in HIV case-finding or incidence (Scenario 1). The minor drop in the first nine years is a result of the improvement in HIV case-finding prior to 2010 resulting in that the number of patients leaving the undiagnosed pool (diagnoses and deaths) is slightly larger than the number of patients entering the pool (new infections).

In Scenario 2, with a 5% annual increase in HIV incidence and no changes in case-finding, the proportion would decrease from 32.0% to 25.2% in nine years and remain stable afterward. In Scenario 3, with a 5% annual decrease in HIV incidence and no change in case-finding, the proportion would increase from 32.0% to 39.2% in nine years and remain stable afterward.

An expansion of HIV testing will result in an increase in case-finding, i.e., an increase in case detection rate. However, when it has been fully implemented and is no longer in a state of expansion, no further increase in case-finding would be expected, and the case detection rate will be higher and remain stable. With a 10% increase in HIV case-finding (Scenario 4), the case detection rate would increase from 25.0% to 27.5% among persons in their first year of infection and from 10.07% to 11.08% among persons in their second to ninth year of infection, and the proportion of late diagnoses would steadily decrease from 32.0% to 28.1% in nine years and remain stable afterward. In Scenario 5, a 10% increase in HIV case-finding is accompanied by a 5% annual decrease in incidence. The proportion of late diagnoses would decrease from 32.0% to 30.3% in the first year, steadily increase to 35.2 in the next eight years, and remain stable afterward.

In all five scenarios, because the case detection rate and the annual increase or decrease in HIV incidence does not change after 2010, the proportion of late diagnoses would remain unchanged after 2019. A further improvement in case-finding would decrease the proportion but to a less extent than the level of improvement in case-finding, and a larger annual decrease in incidence would increase the proportion.

Sensitivity analysis

With an increase of 20% in HIV case-finding and no changes in HIV incidence, the proportion of late diagnoses would steadily drop from 32.0% to 24.7%; with an increase of 30%, the proportion would drop to 21.7%. With an annual decrease of 10% in HIV incidence and no changes in HIV case-finding, the proportion would steadily increase to 47.1%; with a decrease of 20%, the proportion would increase to 62.5%. With such a dramatic annual decrease (20%) in HIV incidence, there would be only 887 undiagnosed persons and 59 new infections in the USA in 2040. However, the proportion of late diagnoses would still be high (140/224 = 62.5%). To cut the proportion of late diagnoses in half from 32.0% to 16.0, it would take nine years with a 100% improvement in case-finding, by assuming an annual decrease of 10% in HIV incidence from the expansion of HIV testing (data not shown in table or figure).

Discussion

Using a mathematical model, we show that the high proportion of late HIV diagnoses is likely to stay in the USA, and both HIV case-finding and HIV incidence affect the proportion of late diagnoses. The unchanging nature of the proportion of late diagnoses lies with the limitation of the measure itself. The fact that both the numerator and the denominator of the proportion are affected by HIV case-finding makes it less sensitive to the changes in case-finding. An increase in HIV case-finding would reduce the number of late diagnoses because more ninth year infections are diagnosed, leaving fewer undiagnosed cases to enter next year as tenth year of infection, i.e., a smaller numerator, but the number of non-late diagnoses would also be smaller because more first to eighth year infections are diagnosed, leaving fewer undiagnosed cases to enter next year as second to ninth year of infection, i.e., a smaller denominator.

A decrease in HIV incidence can drive up the proportion of late diagnoses by having fewer new infections enter the undiagnosed pool and fewer new infections diagnosed. Because the number of late diagnoses is not immediately affected by a change in HIV incidence, if there are no changes in HIV case-finding, fewer new infections would mean fewer new diagnoses and a relatively larger proportion of late diagnoses observed in the few years after the incidence decline.

People reduce risk behaviors after learning their HIV-positive status (Marks, Crepaz, Senterfitt, & Janssen, 2005; Weinhardt, Carey, Johnson, & Bickham, 1999), and they can also reduce their transmission risk by receiving antiretroviral treatment (ART) and suppressing their HIV viral load (Cohen et al., 2011; Quinn et al., 2000). A large proportion (49%) of new infections in the USA is transmitted by undiagnosed HIV-infected persons (Hall, Holtgrave, & Maulsby, 2012). Increase in HIV case-finding may be able to reduce HIV incidence by removing people from the undiagnosed to the diagnosed pool and linking them to HIV care and treatment. This makes the proportion of late diagnoses more difficult to interpret because an improvement in case-finding can both reduce the proportion by diagnosing more nonlate infections and increase the proportion by reducing HIV incidence.

Because treatment can only start after diagnosis, expansion of ART does not have direct impact on the proportion of late diagnoses. However, it may affect the measure indirectly. Expansion of ART will reduce diagnosed persons' transmission risk and may result in a decrease in HIV incidence, which will increase the proportion of late diagnoses. It is difficult to estimate how long a person has been infected with HIV, especially when he/she acquired the infection long time ago. A late diagnosis is usually determined based on patient's clinical status within one year of diagnosis, not the duration of infection. Because of a better clinical status after treatment, some patients who are diagnosed late based on the duration of infection may appear to be not late, if the definition of AIDS diagnosis within one year of an HIV diagnosis is used for late diagnoses. Therefore, an expansion of ART can cause an underestimate of the proportion of late diagnoses. However, this can be avoided by using a different definition based on patients' clinical status before ART, e.g., CD4 count ≤ 250 cells/mm^3 at diagnosis.

When an effective HIV intervention project is implemented, observers usually expect a steady increase or decrease in one or more indicators, e.g., proportion of youth with consistent condom use, proportion of newly diagnosed patients linked to HIV care within three months, and proportion of patients with a suppressed viral load, during the whole project period (Des Jarlais et al., 2005; Dubois-Arber, Jeannin, Konings, & Paccaud, 1997; Torian, Xia, & Wiewel, 2014; Xia, Nonoyama, Molitor, Webb, & Osmond, 2011). This will likely not occur when the metric used is the proportion of late diagnoses as a measure of the effectiveness of expanded HIV testing. The model shows that the proportion remains stable despite the sustained expansion of HIV testing.

Our model has limitations. First, we assume that if not diagnosed, all patients develop AIDS in the tenth year of infection, no earlier and no later, and define late diagnosis based on patient's clinical status within one year of diagnosis, not the duration of infection. We know that approximately half of all persons with HIV will develop AIDS within 10 years if not treated (Kuo et al., 1991; UK Register of HIV Seroconverters Steering Committee, 1998). By assuming that all develop AIDS in the tenth year, we falsely include late diagnoses who develop AIDS earlier or later, but at the same time, we also falsely exclude late diagnoses who are not in their tenth year of infection but develop AIDS in the year of analysis. The false inclusions and exclusions may cancel each other out and provide a reliable estimate of the number of late diagnoses to be used to calculate the proportion.

Second, we assume a 100% case detection rate among patients in their tenth year of infection. Many patients are diagnosed soon after they develop AIDS, but not all. By assuming a 100% case detection rate, we would overestimate the reduction in the proportion of late diagnoses. For example, our model demonstrates that a 10% increase in HIV case-finding would reduce the proportion of late diagnoses by 6.6%, based on the assumption that 100% of patients are diagnosed when they develop AIDS. An increase in HIV case-finding would increase the denominator but not the numerator. With some patients diagnosed long after they develop AIDS, i.e., after year 10, an increase in HIV case-finding would increase both the numerator and the denominator. In this case, the reduction in the proportion of late diagnoses would be even smaller than we predicted in the model and the trend would be more stable.

Third, for simplicity reasons, we assume that the case detection rate would increase in the first year and remain at the higher rate afterward but not continue to increase. However, testing expansions typically take more than one year to really have an impact and may, in fact, build momentum over several years (Myers et al., 2012). This means the drop in the proportion of late diagnoses in the first year would be even smaller and the trend would be more stable.

In conclusion, our model shows that the most significant limitation of the measure is that both numerator and denominator are affected by HIV case-finding. We would continue observing a high and stable proportion of late diagnoses in the USA, which may be interpreted as representing a failed testing initiative, if the limitations of this measure are not fully appreciated. The case detection rate used in the model accurately reflects HIV case-finding. We should strive to develop methods to measure it in the real world.

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