Review

A systematic review of limiting antigen avidity enzyme immunoassay for detection of recent HIV-1 infection to expand supported applications

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ABSTRACT

Introduction: The need for detection of new and recent HIV infections is essential for surveillance and assessing interventions in controlling the epidemic. HIV recency assays are one way of providing reliable incidence estimates by determining recent versus non-recent infection. The objective of this study was to review the current body of knowledge of the limiting antigen avidity enzyme immunoassay to expand supported applications through an assessment of what is known and the gaps.

Methods: A search for peer-reviewed literature in PubMed, Embase, and Web of Science Core Collection was conducted using the search term "human immunodeficiency virus and avidity". Non-peer reviewed published reports from the Population-based HIV Impact Assessment Project were also included. These were limited to literature published in English between January 2010 and August 2021.

Results: This search resulted in 2080 publications and 14 reports, with 137 peer-reviewed studies and 14 non-peer reviewed reports that met the inclusion criteria, yielding a total of 151 studies for the final review. There were similar findings among studies that compared the performances of assay manufacturers and sample types. Studies that evaluated various assay algorithms and thresholds were heterogeneous, illustrating the need for context-specific test characteristics for classifying recent infections. Most studies estimated subtype-specific test characteristics for HIV subtypes A, B, C, and D. This was further illustrated when looking only at studies that compared HIV incidence estimates from recency assay algorithms and longitudinal cohorts.

Conclusions: These findings suggest that the current body of knowledge provides important information that contributes towards distinguishing recent and non-recent infection and incidence estimation. However, there are knowledge gaps with respect to factors that influence the test characteristics (e.g., HIV-1 subtype, population characteristics, assay algorithms and thresholds). Further studies are needed to estimate and establish context-specific test characteristics that consider these influencing factors to improve and expand the use of this assay for detection of recent HIV infection.

1. Introduction

While the global community is working towards the 95-95-95 targets, established by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to end the AIDS epidemic by 2030, detecting new and/or recent infections remains essential for surveillance and assessing interventions in controlling the epidemic.[1] According to UNAIDS, in 2020, an estimated 38 million people were living with HIV, including 1.7 million with newly diagnosed infections.[2] Traditional methods for estimating incident infections, such as longitudinal studies, are marked by a variety of challenges.[3] However, HIV incidence assays, sometimes referred to as recency assays or cross-sectional incidence assays, are one way of obtaining reliable estimates while addressing some challenges posed by traditional methods. Briefly, recency assays use biomarkers such as antibody avidity, a function of the immune response maturing over time, to classify HIV-positive specimens as recent or non-recent

infection.[4,5] Currently available recency assays are for research purposes only and are not intended for the diagnosis of HIV infection, with some developed specifically for identifying recent infection and others modified from commercially available HIV diagnostic assays.[6]

Supplemental material 1 provides examples of recency assays that were evaluated using well-characterized samples from the Consortium for the Evaluation and Performance of HIV Incidence Assays.[3] The limiting antigen avidity enzyme immunoassay (LAg), of the seven recency assays evaluated, was considered to be one of the frontrunners. The United States Centers for Disease Control and Prevention (CDC) initially developed LAg and transferred the manufacturing process to Sedia Biosciences Corporation (Portland, Oregon, USA) and Maxim Biomedical, Inc. (Rockville, Maryland, USA), henceforth called Sedia and Maxim, respectively.[7–9]

LAg measures the avidity of HIV-1 antibodies using rIDR-M antigens, which are recombinant proteins that cover the immunodominant region of HIV gp41 from all major subtypes and recombinants of HIV-1 group M, where high- and low-avidity HIV-1 immunoglobulin G (IgG) antibodies bind to the antigen. Dissociation buffer is added to remove low-avidity antibodies. Goat anti-human IgG horseradish peroxidase (HRP) is then added and incubated, which binds to the remaining IgG bound to the microplate. Incubation with tetramethylbenzidine substrate reacts with HRP to generate color and is proportional to the amount of HRP in the well. Optical density (OD) of the plate is read at 450 nm. A normalized OD (ODn) value is calculated for each specimen using calibrator specimens tested on the same plate. Median values of the calibrator are used to perform the calculation: ODn = specimen OD/median calibrator OD. Results at or below 2.0 ODn require confirmatory testing in triplicate. Results from triplicate confirmatory testing with ODn $\leq$ 1.5 are classified as recent infection and ODn > 1.5 are non-recent (i.e., have longstanding infection).[7–9]

The number of HIV-negative participants and HIV-positive participants, classified as recent or non-recent, are transformed into incidence estimates using two test characteristics: 1) mean duration of recent infection (MDRI), the average time an individual is classified as recently infected; and 2) false recent rate (FRR), sometimes referred to as proportion false recent or false recency ratio, which is the probability that an individual who has been infected for longer than a defined time, *T,* is misclassified as recently infected.[3,10]

Recency assays, including LAg, however, have their own unique challenges. In 2008, the World Health Organisation (WHO) established the Working Group on HIV Incidence Assays to address issues and challenges of estimating recency assay-based HIV incidence.[11,12] The group has made great progress in addressing some issues, such as the guidance document on monitoring the HIV epidemic using population-based surveys.[13] However, issues that have not been addressed thus far remain, including: 1) methods for context-specific MDRI and FRR; 2) evaluating the need and role for antiretroviral (ARV) testing in recent infection testing algorithms (RITAs) to estimate incidence; 3) estimating incidence using methods beyond RITAs; and 4) maintenance and development of biorepositories of specimens to further support research and testing of assays and serologically-based incidence estimate strategies.[12]

HIV incidence estimates are essential in evaluating the efficacy and effectiveness of interventions in reducing and preventing transmission in the community. One area of interest where recency assays could be beneficial is in HIV pre-exposure prophylaxis (PrEP) clinical trials to assess new interventions, as reported by the WHO Technical Working Group on HIV Incidence Assays 2011 report.[6] Recency assays estimate the background HIV incidence which potentially serves as an external control counterfactual. The use of high quality incidence estimates in externally controlled trials is an interest supported by the United States Food and Drug Administration.[14] A systematic literature review provides additional insight in bringing the process forward given the need and the increasing interest in the expanded use of recency assays. The objective of this study was to review the literature on the use of LAg to measure HIV incidence, to assess what is known and not known, and provide recommendations for studies that will address knowledge gaps to expand supported applications of LAg.

2. Methods

We conducted a systematic literature search following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[15] This systematic review was not registered with the International Prospective Register of Systematic Reviews (PROSPERO). We used three databases to conduct the search: PubMed, EMBASE, and Web of Science Core Collection. We used the search term "human immunodeficiency virus and avidity" rather than "limiting antigen avidity" to obtain as broad a range as possible of published HIV avidity studies that included the use of LAg. We imported records from these databases into Covidence, an online tool for conducting and managing systematic reviews. Separately, we included non-peer reviewed reports from the Population-based HIV Impact Assessment (PHIA) Project into the final exported dataset. We were unable to import these online reports into Covidence as the reports were unavailable in the databases. Briefly, the PHIA Project conducts nationally representative cross-sectional surveys to assess the current status of national HIV epidemics and the effectiveness of health programs in controlling the HIV epidemic.[16] PHIA surveys used a laboratory-based RITA, including LAg, viral load, and ARV detection, to estimate HIV incidence.[17]

This review focused on studies that were available in English and from January 1, 2010 through August 23, 2021. Initial development of LAg was published in 2010,[7] thus publications prior to 2010 would not be relevant. Abstracts and methods were initially reviewed followed by a full-text review of the studies that met the inclusion criteria. Publications, reports, and conference posters and abstracts were included in the review if LAg was used to conduct a study; those that did not meet the inclusion criteria were removed.

We categorized studies as evaluation or field use and collected relevant data, including LAg manufacturers, locations where blood samples were collected, HIV-1 subtypes, and LAg algorithms and thresholds. Sample collection locations were categorized according to the United Nations online publication of the "Standard Country or Area Codes for Statistical Use".[18] HIV subtypes were categorized as "multiple" if there was more than 1 identified subtype that did not have separate results for the algorithm(s) used or evaluated. Studies with no identified HIV-1 subtype were categorized as "not defined". Studies that evaluated multiple algorithms and/or thresholds for MDRI and/or FRR had separate column entries for each: standalone LAg ODn thresholds of 1.0, 1.5, 2, or other; an algorithm of LAg plus viral load of 1000 copies per milliliter with the abovementioned ODn thresholds, or other thresholds of either assay and other LAg algorithms. We, then, summarized the review of these studies based on topics found among evaluation and field use studies. Lastly, we identified knowledge gaps on the impact of using LAg, with respect to HIV subtypes, key populations, and algorithms or thresholds that should be considered.

3. Results and discussion

3.1. Search results

The search yielded 2080 records and 14 PHIA reports, which include full reports and summary sheets if full reports were unavailable. Records from the database were filtered for English and limited from years 2010–2021, excluding 24 and 669 records respectively (Fig. 1).

Abstracts and methods were reviewed for LAg use and excluded 591 studies. Two hundred thirty-seven records were assessed for eligibility. All 14 PHIA reports were included for this review. Note that four reports came from two countries from two different survey years. This resulted in 151 studies included in this systematic review.
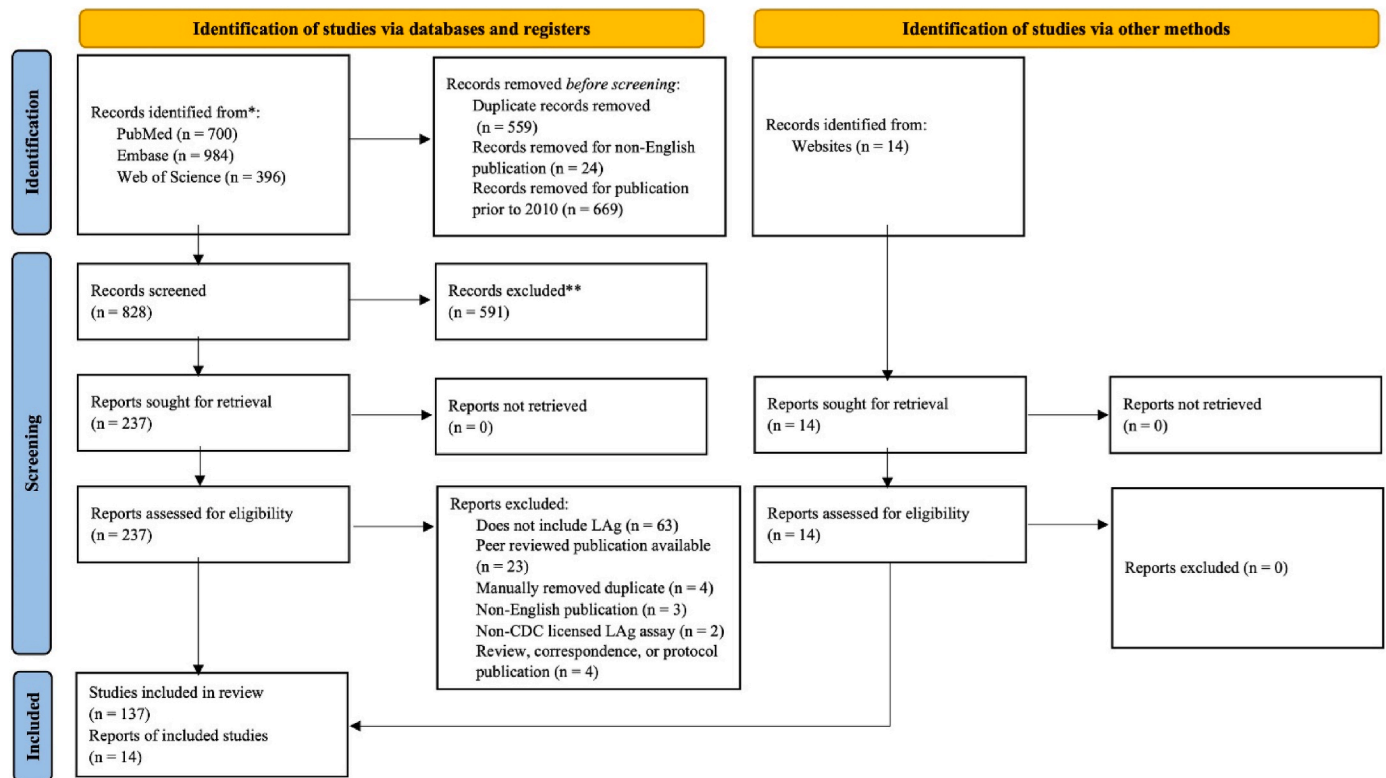
Fig. 1. PRISMA Diagram Abbreviations: CDC, United States Centers for Disease Control and Prevention; LAg, limiting antigen avidity enzyme immunoassay.

3.2. Test kits, geographical regions, and HIV-1 subtypes associated with LAg use

Two of the 151 studies were conducted using kits developed at the CDC: one to further optimize and characterize LAg[5] and the second to evaluate performance of LAg in previously collected study samples of a population with HIV-1 subtype A and D infection[19] (Fig. 2).

Eighty-seven studies used only Sedia-manufactured kits while 9 studies used only Maxim-manufactured kits. Three studies compared the performances of the two manufacturing companies of LAg. Lastly, we could not identify the assay manufacturer for 38 studies which were categorized as "not defined". Twelve studies did not state the geographic locations where samples were collected from (Fig. 3).

Among the 151 studies, 71–50 field use and 21 evaluation – did not define which subtype(s) were used; 110 HIV-1 subtypes were identified or used (Fig. 4).

The following sections reflect topics among studies that were categorized as either evaluation or field use.

3.3. Comparing performance of assay manufacturers

Three of the 71 evaluation studies compared the performance of the Maxim and Sedia LAg. Within each study, both assays were tested using the same sample panel. Similar findings were reported: 1) there were calibrator differences between the two assay manufacturers and 2) ODn readings in the Maxim assay were lower compared to Sedia, indicating that Maxim assays had higher MDRI estimates than Sedia.[20–22] These studies noted that investigators must be aware of the differences between the two assay manufacturers when planning studies that use LAg and recommend that only one assay manufacturer should be used to conduct an entire study as this will have implications on how the data are analyzed, interpreted, and compared.[21,22] These findings highlight the need for publications to specify the assay manufacturer used to increase the validity of interpretation and comparison of results (i.e.,
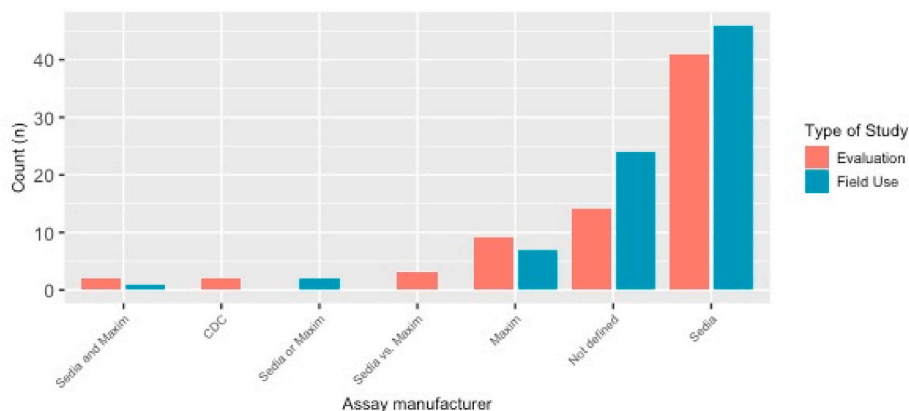

Fig. 2. Number of studies by assay manufacturer abbreviations: CDC, United States centers for disease control and prevention.
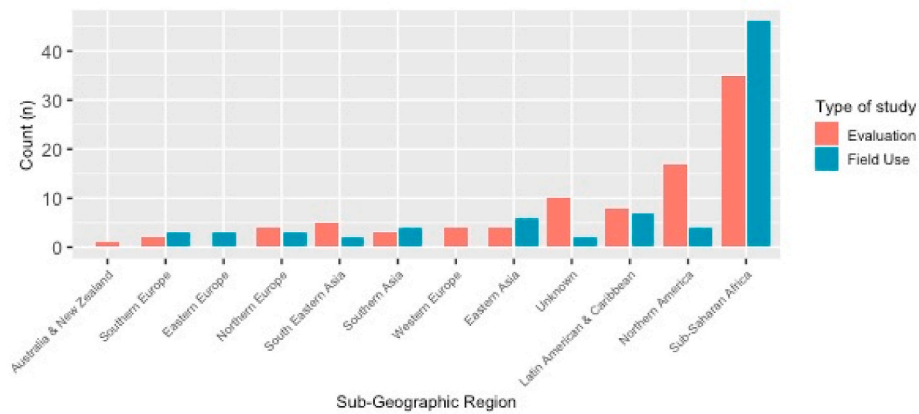
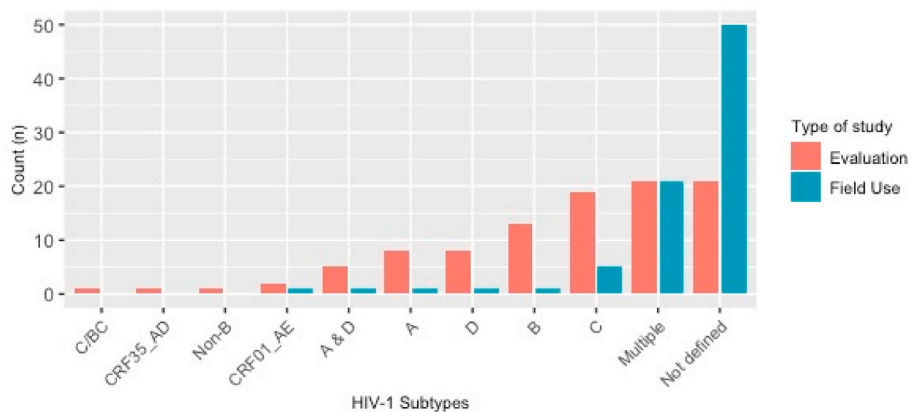**Fig. 3.** Number of studies by sub-geographic region.

Fig. 4. Number of Studies by HIV-1 Subtype.
Note that some studies may have identified and/or used more than one subtype.

results from Maxim-produced kits should not be compared to results from Sedia-produced kits unless the same exact samples are used).

3.4. Comparing sample types

Four of the 71 evaluation studies compared the results of various sample types used in LAg. Within each study, matched plasma (or serum) and DBS samples were collected to determine the correlation of these sample types. Four studies reported that results for DBS and plasma (or serum) had good correlation and agreement,[23–26] while three of the four studies found that there was greater variability observed in the higher range of ODn for both.[23–25] Additionally, one of the three studies compared the average ODn difference of matched plasma and DBS, where both sample types were stored at −80 °C or plasma was stored at −80 °C and DBS was stored at 25 °C. Results showed that the average ODn difference among matched frozen plasma and room temperature DBS were much higher compared to when both sample types were frozen.[23] These findings indicate that studies could use both sample types within the same study. However, investigators must ensure that the collected samples are stored at proper temperatures to ensure good correlation and confidence in comparing study results.

3.5. Comparing observational and RITA incidence estimates

Nine of the 151 studies estimating HIV incidence compared observational prospective incidence to one or more RITAs. These studies were part of surveys or trials, with six of the nine conducted in sub-Saharan Africa and the other three in North America. Subtypes used to

estimate observational and RITA HIV incidence included A and D in the same survey, B, and C.[27–33] RITA incidence for these studies had 95% confidence intervals (95% CI) that either included or did not include the observed incidence point estimate (Supplemental material 2). Point estimates using RITA also changed depending on the algorithms and thresholds used. For example, *Laeyendecker* et al. compared observed incidence from the 2012–2013 Rakai Community Cohort Study to several RITAs.[27] Observed incidence estimates from the survey was 0.66/100PY (95% CI 0.52–0.83). RITAs used included: LAg ODn less than 1.5 with viral load greater than 1000 copies per milliliter (cp/mL) (2.55/100PY (95% CI 1.51–3.59)) and subtype A and D specific MDRI and FRR LAg with viral load with the same thresholds (0.67/100PY (95% CI 0.00–1.68)). The subtype-specific adjusted algorithm had a closer incidence estimate with a confidence interval that included the observed incidence point estimate compared to the non-adjusted algorithm.

3.6. LAg algorithms and thresholds to estimate MDRI and FRR

One or more LAg algorithms and thresholds were evaluated to estimate MDRI and FRR among the 71 evaluation studies. This included studies that compared Maxim- and Sedia-produced MDRI and FRR estimates as well as those that were then used to estimate incidence. These studies evaluated many algorithms for various HIV-1 subtypes and/or ODn thresholds (Tables 1 and 2).

More studies evaluated standalone LAg (i.e., LAg alone, not part of a RITA) ODn thresholds of 1.5 units for MDRI (39 of 105) and FRR (48 of 106) compared to other thresholds for standalone LAg. This was similar

Table 1
Number of LAg algorithms and thresholds evaluated for estimating MDRI based on assay manufacturer and HIV-1 subtype Abbreviations: CDC, United States Centers for Disease Control and Prevention; cp/mL, copies per milliliter; HIV, human immunodeficiency virus; LAg, limiting antigen avidity enzyme immunoassay; ODn, normalized optical density; VL, viral load Studies may have evaluated more than one algorithm using the same manufacturer or multiple manufacturers using the same algorithm. Other LAg + VL algorithm thresholds include studies that used only LAg and viral load at other thresholds that are not reflected above. Other LAg algorithms include studies that used LAg in addition to other assays to estimate MDRI.

Manufacturer and HIV-1 Subtype	LAg ODn ≤ 1.0	LAg ODn ≤ 1.5	LAg ODn ≤ 2.0	Other LAg Threshold	LAg ODn ≤ 1 + VL > 1000 cp/mL	LAg ODn ≤ 1.5 + VL > 1000 cp/mL	LAg ODn ≤ 2.0 + VL > 1000 cp/mL	Other LAg + VL Threshold	Other LAg Algorithm
CDC									
A & D	1	1	1	1					
B	1	1	1	1					
C	1	1	1	1					
Multiple	1	1	1	1					
Sedia									
A	1	4	2	1	1	2	2	2	
A & D	1	1	1	1					
B	2	4	3	2	2	3	2	1	2
C	2	5	3	3	2	5	3	2	2
C/BC	1	1	1	1					
CRF01_AE	1	1	1	1					
D	1	4	2	1	1	2	2	2	
Multiple	2	5	3	2	1	2	1	2	2
Sedia and Maxim									
C					1				
Sedia vs. Maxim									
A	1	1	1	1	1	1	1	1	
B	1	1	1	1	1	1	1	1	
C	1	2	1	1	1	2	1	1	
D	1	1	1	1	1	1	1	1	
Multiple	1	1	1	1	1	1	1	1	
Not defined									
A		1							
C		2							
D		1							
Total	**20**	**39**	**25**	**21**	**13**	**20**	**15**	**14**	**6**

among studies that used LAg ODn threshold of 1.5 with viral load threshold of greater than 1000 cp/mL (20/62 for MDRI and 24/67 for FRR). This may reflect the manufacturer's recommendation within the product insert of a 1.5 ODn threshold.[8,9] There were studies that used other algorithms that included additional recency assays (e.g., Bio-Rad Avidity assay), CD4$^+$ T cell count, detection of ARVs, or some combination thereof with or without viral load.[25,29,31,32,34–41]

The heterogeneity of these studies illustrates the need to consolidate information related to factors that influence MDRI and FRR estimates. *Kassanjee* et al.[3,10] demonstrated these differences in MDRI and FRR estimates based on study population characteristics, HIV-1 subtype, and assay time cut-off. These factors, in addition to the assay manufacturer, must be considered to appropriately estimate MDRI and FRR and validly compare the estimates across studies done in similar settings.

3.7. Measurement of HIV incidence in the field

Twenty-six of the 80 studies used LAg in the field to measure HIV incidence. These included peer-reviewed studies conducted in various sub-regions, including Sub-Saharan Africa, Latin America and the Caribbean, Eastern Europe, and Western Europe. There was no consistency among these studies on the LAg algorithm to measure HIV incidence. For example, there were studies that used the following: LAg as a standalone assay[42]; an algorithm consisting of LAg plus viral load (VL)[43–45]; and other LAg algorithms.[46–52] Fourteen of these studies were PHIA surveys; all fourteen surveys were conducted in Sub-Saharan Africa and used consistent methodology, namely LAg plus VL and ARV detection to measure HIV incidence.[17] However, this could be a result of testing various algorithms over time for detection of recent infection for estimating incidence.

The thresholds used to measure HIV incidence were similar across these studies, except for the one study that used LAg as a standalone assay. These consisted of a LAg ODn less than 1.5, viral load greater than 1000 cp/mL when used, and an absence of ARV when used. However, it should be noted that the manufacturer's recommended MDRI was used almost consistently across peer-reviewed studies and PHIAs, unless predefined by an estimated MDRI from a prior study. This suggests that the characteristics of the population were similar in each of the settings where samples were collected. As mentioned in the previous subsection regarding estimation of MDRI and FRR, factors that influence these variables should be considered to measure HIV incidence with better precision and accuracy.

3.8. Knowledge gaps on areas that impact use of LAg

Six HIV-1 subtypes, including two circulating recombinant forms (CRFs), consisting of A, B, C, D, CRF01_AE, and CRF35_AD, were used to estimate subtype specific MDRIs and FRR. Few studies were conducted on subtypes CRF01_AE and CRF35_AD compared to subtypes A, B, C, and D. However, there are other prevalent subtypes distributed among various parts of the world, including F, CRF02_AG, and CRF07_BC.[53] The lack of MDRI and FRR estimates for these prevalent subtypes suggests that use of LAg as a measurement of HIV incidence could be affected, given that some sub-regions are dominated by multiple HIV-1 subtypes. For example, subtype B predominated in North America while in Sub-Saharan Africa, subtypes A, C, and D predominated.[53]

Among the 151 studies included in this review, study populations included key populations, such as MSM, *trans-* and *cis*-gender women, and persons who inject drugs. However, there were few to no LAg studies performed in key populations where humoral immunity of HIV infection over time are not as well understood. These populations include: 1) those who have early initiation of antiretroviral therapy (ART) during acute HIV infection; 2) clinical trial vaccine recipients; and 3) pregnant women. For example, we found two studies done using samples collected from the Zimbabwe Vitamin A for Mothers and Babies Trial, where postpartum women and their new-borns were recruited and

Table 2

Number of LAg algorithms and thresholds evaluated for estimating FRR based on assay manufacturer and HIV-1 subtype Abbreviations: CDC, United States Centers for Disease Control and Prevention; cp/mL, copies per milliliter; HIV, human immunodeficiency virus; LAg, limiting antigen avidity enzyme immunoassay; ODn, normalized optical density; VL, viral load Studies may have evaluated more than one algorithm using the same manufacturer or multiple manufacturers using the same algorithm. Other LAg + VL algorithm thresholds include studies that used only LAg and viral load at other thresholds that are not reflected above. Other LAg algorithms include studies that used LAg in addition to other assays to estimate FRR.

Manufacturer and HIV-1 Subtype	LAg ODn ≤ 1.0	LAg ODn ≤ 1.5	LAg ODn ≤ 2.0	Other LAg Threshold	LAg ODn ≤ 1 + VL > 1000 cp/mL	LAg ODn ≤ 1.5 + VL > 1000 cp/mL	LAg ODn ≤ 2.0 + VL > 1000 cp/mL	Other LAg + VL Threshold	Other LAg Algorithm
CDC									
A	1		1						
D	1		1						
Maxim									
C									1
Multiple		1		1		1		1	1
Not defined		1				1			1
Sedia									
A	1	4	2	1	1	2	2	1	
A & D	1	1	1	1		1			
B	2	5	3	2	1	2	2	1	
C	2	5	3	2	2	4	3	2	1
C/BC	1	1	1	1					
CRF01_AE	1	2	1	1		1			
CRF35_AD		1							
D	1	4	2	1	1	2	2	1	
Multiple	2	8	3	2	1	2	1	2	2
Non-B		1							
Not defined		2							
Sedia vs. Maxim									
A	1	1	1	1	1	1	1	1	
B	1	1	1	1	1	1	1	1	
C	1	2	1	1	1	2	1	1	
D	1	1	1	1	1	1	1	1	
Multiple	1	1	1	1	1	1	1	1	
Not defined									
A		2						1	
A & D						1			
C		2				1		1	
D		2						1	
Not defined								1	1
Total	**18**	**48**	**23**	**17**	**11**	**24**	**15**	**17**	**7**

followed, to observe effects of maternal and/or neonatal vitamin A in reducing HIV transmission, comorbidities, and child mortality.[54,55] Both studies found that MDRI and FRR estimates were lower compared to other studies. This further demonstrates the need to understand how HIV infection among these key populations affect the use of LAg in identifying recent infections.

3.9. Likely importance of using context-specific LAg parameters

Valid comparisons of LAg-based incidence estimates across different studies likely depend on context. MDRI and FRR of the LAg avidity recency test appear to depend on the population under study (MSM, cisgender heterosexual women, general population, etc) and the circulating HIV-1 subtypes in the region where the study is being conducted. Various combinations of ODn and VL have been used to estimate FRR depending on both assay manufacturer and predominant circulating HIV-1 subtype (Table 2). LAg-based incidence estimates using different combinations of test characteristics can provide different incidence estimates even when used on the same population (**Supplemental material 2**).

4. Conclusions

In this systematic review of peer-reviewed literature and non-peer reviewed PHIA reports published since the initial development of LAg, we describe the use of the LAg assay for the measurement of HIV incidence and identification of HIV risk factors within a specific population. This review complements the findings of *Facente* et al.*'s* systematic review of the use of recency assays for HIV incidence estimation.[56] In

addition, LAg has the potential to be used in other study designs, such as HIV PrEP clinical trials, where measuring HIV incidence is critical for assessing the efficacy of new prevention modalities.[6] The potential use in HIV PrEP clinical trials could expand the available options of prevention modalities. The Forum for Collaborative Research PrEP Project established the Recency Assay Working Group, composed of stakeholder representatives from academia, industry, and regulatory agencies, focusing on the use of recency assays to estimate the background HIV incidence that could serve as a counterfactual for PrEP studies.[57]

Limitations for this review include limiting the search of peer-reviewed literature to only three databases, multiple search terms were not used to identify more unique and duplicate results, and the inclusion of PHIA reports as the only non-peer reviewed source.

Although LAg has been demonstrated to be an effective tool, knowledge gaps do exist. These recommendations would begin to address issues and expand supported applications of LAg:

- Estimating MDRI and FRR for HIV-1 subtypes (non-B and C) that are prevalent in different regions;
- Evaluating the impact of classifying recent infections in those initiated in early ART and pregnant women, where maturity of humoral immunity in response to HIV infection may be affected; and
- Establishing context-specific LAg thresholds and algorithms for better comparisons of study results

These studies will increase our understanding on the accuracy and precision of LAg and the reliability of the interpretation of these results. However, frequency of HIV testing among the population of interest should be considered. Those who would be diagnosed as HIV-positive

within the designated time cut-off of the recency assay may be less likely to participate in studies. This, therefore, reduces the person-time contribution of recently infected persons towards incidence calculations. Reliability of these interpretations would be influenced in populations that have high frequency of HIV testing, which could then affect HIV incidence estimates.

In summary, the current body of knowledge for the evaluation and use of LAg in the field has grown, but there is still missing information. Many factors influence MDRI and FRR estimates (e.g., HIV-1 subtype, assay manufacturer, and the algorithm and/or threshold used), which impacts the classification of recent and non-recent infection. Additional studies in these areas will give insight on the observed differences in antibody maturation for specific contexts. Although the intended use of LAg is for research purposes only, the types of research that can be done by utilizing this assay continues to expand and inform how HIV incidence changes over time and implement more targeted approaches for interventions in controlling the epidemic. However, LAg, and recency assays in general, could potentially be used as a diagnostic tool as we develop more recency assays with the ability to detect acutely infected individuals that have not yet seroconverted.[58] Although more rigorous testing and research is needed for recency assays to be used diagnostically, it should not be a barrier given the potential public health benefits that this would provide.

Authors' contributions

JL: Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review and editing.

NM: Data curation; Formal analysis; Writing – original draft; Writing – review and editing.

JM: Writing – review and editing.

JJ: Writing – review and editing.

NP: Conceptualization.

VM: Conceptualization; Supervision; Writing – review and editing.

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Data statement

Data collected for this paper and the visualization can be found here: https://github.com/nick-murdock/lagreview.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jve.2022.100085.

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