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Residual risk estimation of HBV, HCV or HIV infection after ID-NAT testing of a blood unit



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FLOW OF THE PRESENTATION

- I. Definitions**
- II. Viral kinetics**
- III. Causes of non-detection of viral infection in blood donors**
- IV. Viral epidemiology in donors**
- V. Estimation of Residual risk**
- VI. Adjustment factors**



I. DEFINITIONS

New & Old...

- **Incidence:** The rate of newly acquired infection identified over a specified time period in a defined population.
- **Prevalence:** The rate of identified infection, including both past and present infections, at a specified point in time in a defined population.



Sensitivity

- **Analytical sensitivity:** The smallest amount of the target marker that can be precisely detected by an assay;
 - Expressed as the Limit of Detection
- **Diagnostic sensitivity:** The probability that an assay gives a positive result in human specimens containing the target marker (being true-positive).



Window period

- **Diagnostic window period:** The time interval from infection to the time point when a blood sample from that infected person first yields positive result in a diagnostic or screening assay for that agent.

Window period (Contd...)

- The diagnostic window period consists of **two phases**:
 - **Eclipse period**: The first period of viral replication in the target tissue without presence in peripheral blood;
 - **Viraemic phase**: The eclipse period is followed by the ramp up phase where the virus concentration increases exponentially in the blood.



Diagnostic window periods

- In the context of blood safety, the viraemic phase within the diagnostic window period is relevant.
- The **start of the infectious window period** is defined as when the concentration reaches **1 virus particle in 20 ml of plasma** (the volume co-transfused with a PRBC unit suspended in additive solution).



Diagnostic window periods

- The length of the diagnostic window period of screening assay, depends on,
 1. The screening **marker,**
 2. The screening assay **category,**
 3. The **sensitivity** of the assay used
 4. The **replication kinetics** of the virus during early infection.



Window period vs. Residual Risk

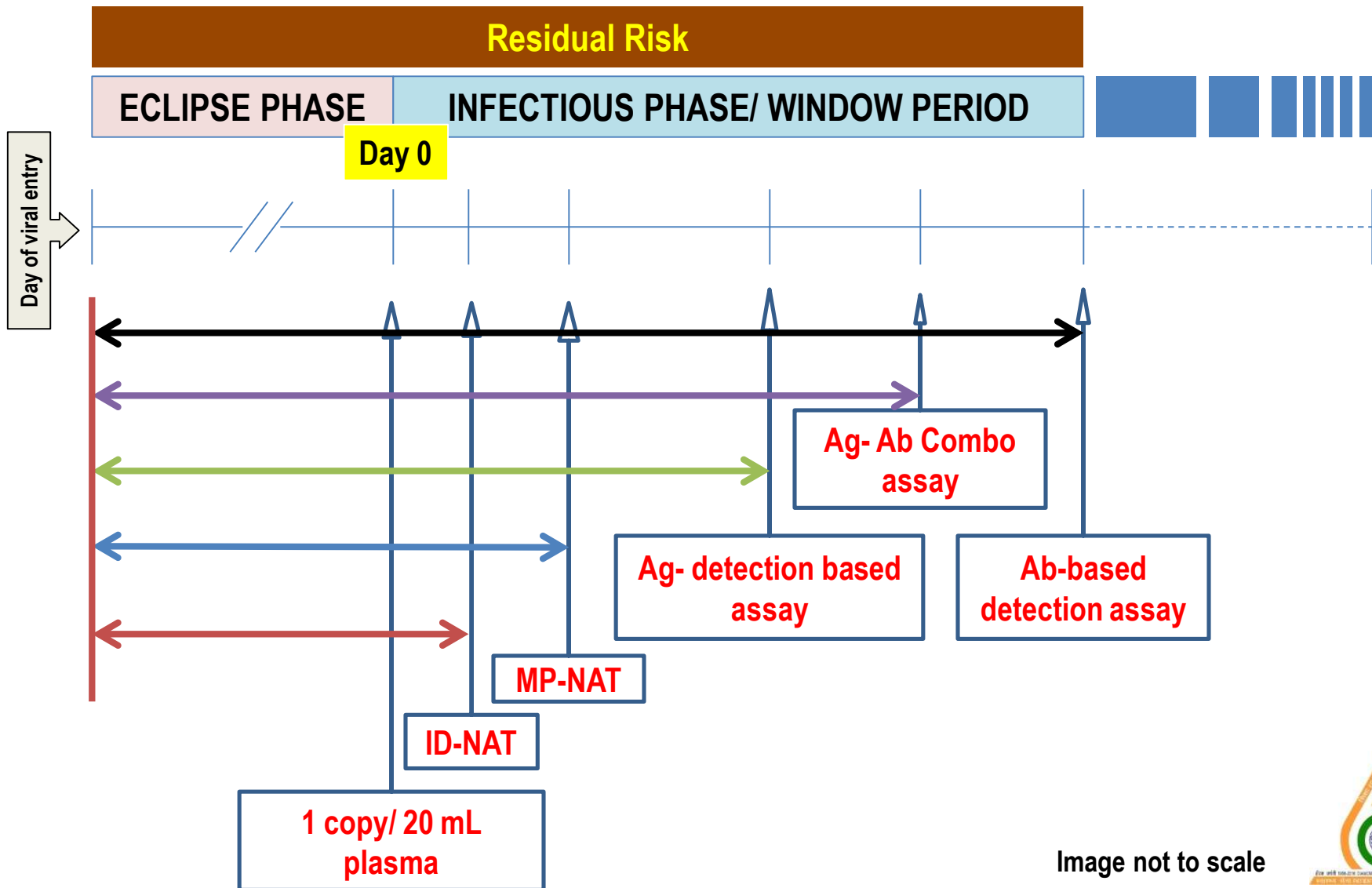


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Risk remains!!!

- The residual risk for missing viral infections by any screening assay is mainly due to
 - The **viraemic phase of its diagnostic window period**, which varies between different assay categories.
- Another component of the residual risk is the virus epidemiology of the donor population;
 - The frequency of new infections (**incidence**) in donors determines the probability for window period donations.



Residual risk

- The residual risk of HIV, HBV or HCV infections in blood or plasma donations is defined as the probability of a viraemic donation from a donor infected with one of these blood borne viruses not being detected by the routine screening assay(s).

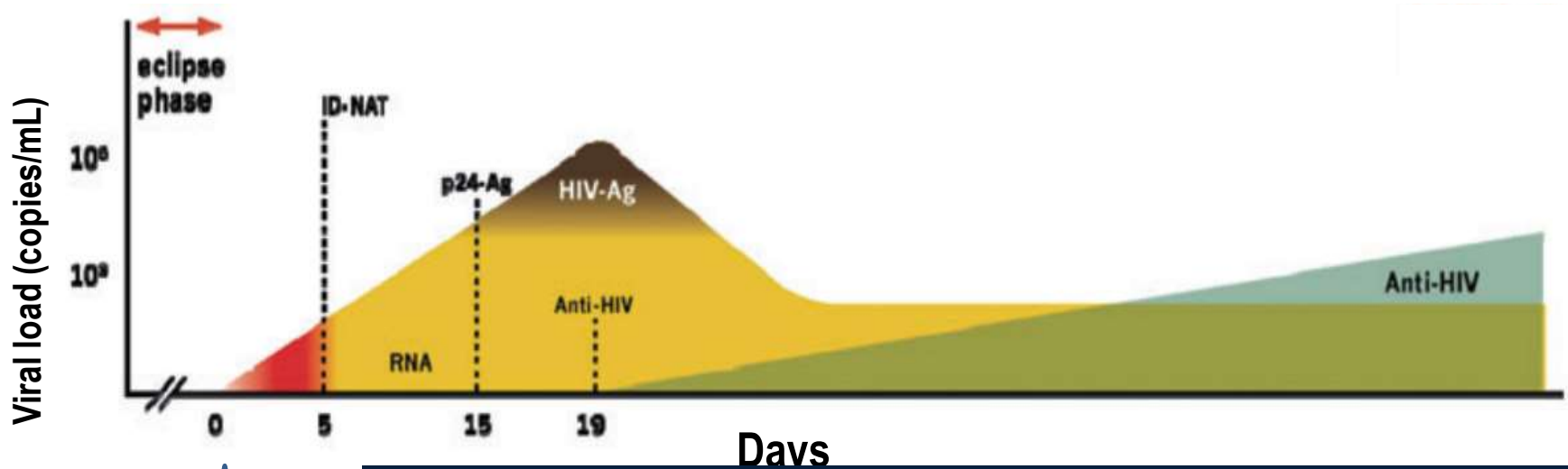


Methods of estimation: Residual Risk

- **Incidence-Window period (I-WP) model**
 - Incidence based on repeat donors donation history,
 - Incidence based on serology based assay yield cases.
 - Incidence based on NAT-yield cases.
- **Mathematical model**

II. VIRAL KINETICS

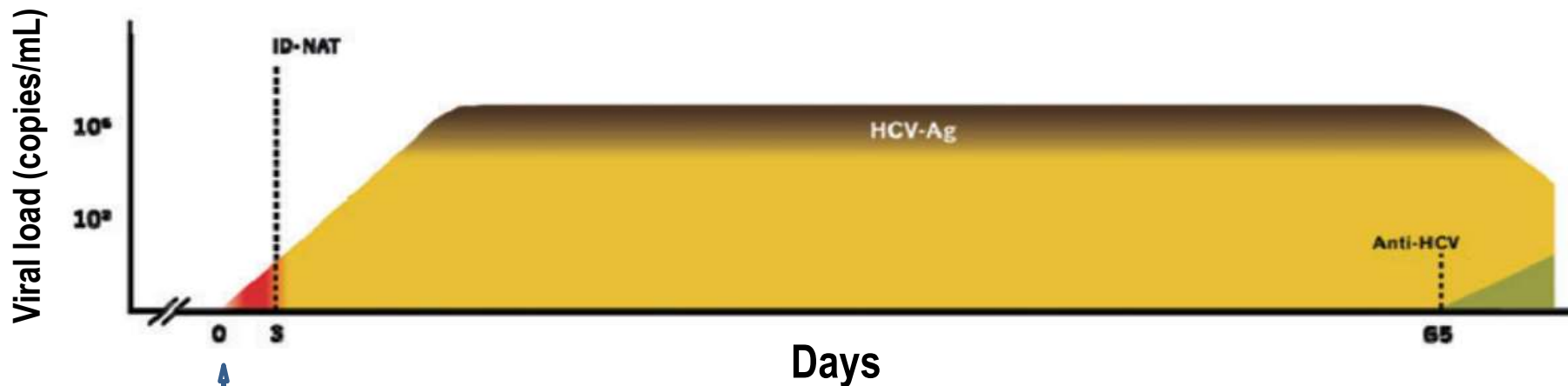
HIV



1 copy/ 20
mL plasma

- **Red shaded area:** Relative probability of infectivity of units collected in the pre-ID NAT window period
- **Yellow shaded area:** Viral nucleic acid concentrations
- **Gray shaded area:** Timing of detection of high-level viremia by antigen assays.
- **Blue-gray shaded area:** Detection by antibody assays.

HCV

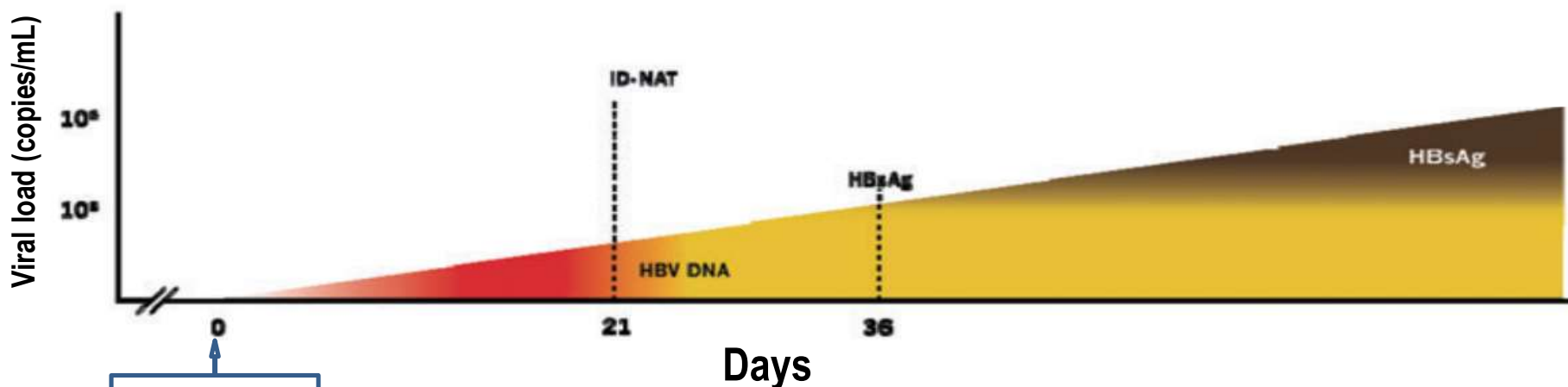


1 copy/ 20
mL plasma

- Red shaded area: Relative probability of infectivity of units collected in the pre-ID NAT window period
- Yellow shaded area: Viral nucleic acid concentrations
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- Blue-gray shaded area: Detection by antibody assays.



HBV



- Red shaded area: Relative probability of infectivity of units collected in the pre-ID NAT window period
- Yellow shaded area: Viral nucleic acid concentrations
- Gray shaded area: Timing of detection of high-level viremia by antigen assays.
- Blue-gray shaded area: Detection by antibody assays.



III. CAUSES OF NON-DETECTION OF VIRAL INFECTION



Causes of viral non-detection

1. Assay failures,
2. Viral variants,
3. By donors being in the viraemic phase of diagnostic window period with negative antibodies or antigenaemia,
4. Eclipse phase of window period.



Assay Failure

- Due to viral variants escaping detection
 - e.g Antibodies not detecting antigen of mutant virus
- The assay performance in the screening laboratory
 - e.g. Deficiencies of instrument or software.

Confirmation of screening results for residual risk estimation

- Only reactive screening test results subsequently confirmed as true positive should be taken for the estimation of residual risk.
- Confirmation by:
 - HIV: Western blot or immuno-blot
 - HCV: Immuno-blot
 - HBV: HBsAg neutralisation assay

Residual risk estimation and Problem in India

- **If no confirmation is performed, residual risk estimations based on reactive test results represent a worst case scenario and may considerably overestimate risks.**

IV. VIRUS EPIDEMIOLOGY IN DONORS



Repeat donors

- Any confirmed positive screening test result indicates a new infection having likely occurred during the **Inter-Donation Interval (IDI)**, the time period between the most recent donation (TTI: Reactive) and the previous donation (TTI: Non-reactive).
- However it is also possible that **the previous donation** (tested negative) was **drawn in the diagnostic window period** of the screening assay.



Repeat donors

- Smaller IDIs increase the probability of a viraemic window period donations tested negative in the screening assay.
- **Hence the risk of a screening assay to miss a viraemic window period donation is defined as the length of the viraemic window period divided by the average IDI.**



First time donors

- Positive screening test results in first time donors may be an indication of infections due to
 1. **Prevalent infections:** easily detected by high quality screening assay(s) without assay failures
 2. **Incident infections:** the major contribution to the residual risk of window period infections.



V. ESTIMATION OF RESIDUAL RISK



Estimation of Incidence

$$\text{Incidence} = \frac{\text{Number of repeat donors tested positive during one year}}{\text{Total number of repeat donors in the same year}} \times 100\,000 \text{ population}$$



Factors affecting Residual Risk estimation

- Incidence in the repeat donor population.
- Inter-donation intervals (IDIs).
- The length of the viraemic phase of the diagnostic window period for the assay used.

Residual Risk estimation: HIV and HCV

$$RR = \frac{vDWP}{IDI} \times \frac{\text{number of seroconverters among repeat donors}}{\text{number of donations from repeat donors}}$$

- RR: Residual Risk
- vDWP: Viraemic phase of Diagnostic Window Period of the screening assay
- IDI: Mean Inter-Donation Interval of all repeat donors



VI. DEVELOPMENT OF ADJUSTMENT FACTORS FOR RESIDUAL RISK ESTIMATION



Adjustment factor: HBV incidence

- HBV NAT conversion or seroconversion in repeat donors may be missed due to
 - The **transient viraemia and antigenaemia** in HBV infections (95%).
 - The probability of missing such transient viraemia and/or antigenaemia depends on **the inter-donation intervals (IDIs) and assay sensitivity.**



Adjustment factor: HBV incidence

$$P = 95\% \times \frac{\text{HBV DNA detection period}}{\text{IDI}} + 5\%$$

- P: The probability of detection of HBV viremia by NAT testing
- HBV-DNA detection period: **ID-NAT (90 days)**; MP-NAT (70 days)
- IDI: Inter-Donation Interval
- 5%: Donors with **chronic** viremia or antigenaemia.
- 95%: Donors with **transient** viremia or antigenaemia.



Adjustment factor: First time donor incidence

- Incidence data specific to the first time donor population: Unavailable (most of the time)
- Assume **3-fold higher** incidence of virus infections as the worst case for this sub-population w.r.t the repeat donor sub-population of the same blood establishment.



Adjustment factor: Inter-donation interval (IDI)

- For high incidence settings, the mean IDI of the NAT converting repeat donors may be compared with the mean IDI of non-infected repeat donors.
- Then, residual risk estimation is adjusted by **Relative IDI Difference**.

$$\text{IDI}_{\text{High incidence setting}} = \left[\frac{\sum \text{IDI}_{\text{Non-reactive repeat donors}}}{N_{\text{Non-reactive repeat donors}}} - \frac{\sum \text{IDI}_{\text{Reactive repeat donors}}}{N_{\text{Reactive repeat donors}}} \right]$$



Take Home Message

- The impact of **global viral epidemiological differences** on **blood safety** needs to be assessed together with the **sensitivity of the testing strategy** applied.
- These estimations may be used for
 - Strategic decisions on **choice of assays** to interdict TTI.
 - **Cost benefit analysis.**



Further readings...

- **WHO guidelines on estimation of Residual risk of HIV, HBV and HCV infections via cellular blood components and plasma.**

WHO/BS/2016.2283.

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- Kupek E. Residual Risk of Hepatitis-B-Infected Blood Donations: Estimation Methods and Perspectives. *ISRN Infectious Diseases*. Article ID 839896, 15 pages. <http://dx.doi.org/10.5402/2013/839896>.



Thank you

Blood transfusion safety: Prevention strategies

- 1. Selection of voluntary, non-remunerated blood donors
(VNRBD)**
- 2. Evaluation of medical and personal history**
- 3. Confidential unit exclusion**
- 4. Meticulous TTI screening (Serology and/or NAT)**
- 5. Pathogen Reduction/ inactivation technology**
- 6. Rational use of blood and blood components**



Screening assay categories

- Rapid diagnostic tests
- Antibody assays
- Combo assays
- Antigen assays
- Nucleic acid amplification technique (NAT) based assays

NAT assays are generally able to detect a recent infection prior to antigen assays, followed by combination assays and antibody assays.



Viral replication kinetics

	HIV	HCV	HBV
Doubling time	20 hrs.	10.8 hrs.	2.6 days
Viral load (IU/ mL)	10^7	10^8	10^{10}
Sensitivity of assay	NAT > Ag only assay > Ag-Ab combo assay	NAT > Ag only assay > Ag-Ab combo assay	NAT > Ag only assay



Viraemic phase of the diagnostic window period

Length of the viraemic phase of the diagnostic window period for assays (in days)

	ID NAT	MP NAT	Antigen EIA / CLIA	Combo EIA / CLIA	Antibody EIA / CLIA	Antigen RDT	Combo RDT	Antibody RDT
HIV	4	11	14	16	21	-	20	28
HBV	14	37	42	-	-	55	-	-
HCV	3	7	9	38	60	-	-	80

Virus concentrations during diagnostic window period

- For risk modelling of contamination, the maximum virus concentrations that can be detected in the respective window periods are relevant.

Maximal viral load in the viraemic phase of the diagnostic window period (IU/ml)					
	ID NAT	MP NAT	Antigen EIA / CLIA	Combo EIA / CLIA	Antibody EIA / CLIA
HIV	150	2400	2×10^4	10^5	10^7
HBV	24	384	10^3	-	-
HCV	30	480	10^4	5×10^6	10^8