Early loss of measles antibodies after MMR vaccine among HIV-infected adults receiving HAART

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ARTICLE INFO

Article history:
Received 10 June 2009
Received in revised form 1 September 2009
Accepted 16 September 2009
Available online 30 September 2009

Keywords:
HIV
Measles
Immunization

ABSTRACT

Objective: The objective of the study was to evaluate the immune response to measles vaccine of HIV-infected adults in comparison to HIV non-infected adults.

Design: We conducted a cross-sectional study to identify adults lacking measles antibodies. 26 HIV-infected patients and 22 controls found to be measles seronegative in the cross-sectional study, received the MMR vaccine. We prospectively followed patients and measured measles antibodies, and cellular proliferative responses against measles antigens. We registered all adverse events at baseline, 3 and 12 months after vaccination.

Methods: We determined measles antibodies by ELISA and cellular proliferative response in PBMC’s at baseline, and repeated measurements at 3 and 12 months after immunization.

Results: The humoral immune response to the vaccine between HIV-infected adults and the HIV-uninfected group was not statistically different at 3 months (81% vs. 86% respectively). One year after vaccination, a higher proportion of HIV-infected adults had lost measles antibodies in contrast to controls. The cellular response was not statistically different between the groups at baseline, 3 and 12 months after immunization despite the waning of antibodies at 12 months. No severe adverse events were observed. Most patients were receiving HAART and had a mean CD4+ cell count of 496 cells/mL.

Conclusions: The initial humoral immune response to measles vaccine was not different between HIV-infected adults and HIV-uninfected adults. However, HIV-infected adults have a rapid decline of measles antibodies despite their high CD4+ cell count and sustained cellular proliferative response.

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1. Introduction

HIV-infected adults may receive the measles vaccine either as part of travel-related immunization [1], or during supplementary immunization activities (SIA) routinely or during ongoing outbreaks [2,3]. The latter are generally offered through massive immunization campaigns [2,4–7]. However, little is known about the safety and efficacy of this vaccine in HIV-infected adults and the measles immunization recommendations for them are based in extrapolations from available data in children [8,9].

The application of measles vaccine to asymptomatic HIV-infected children is considered to be safe [2,10–12]. The initial humoral immune response it elicits might be similar to that achieved by HIV-uninfected children [10], although seroconversion rates range from 25% to 90% [4–7,10,13–16]. However, little is known about the long-term persistence of measles antibodies after vaccination of HIV-infected subjects, and most of the previous studies have been conducted in children or in adults not receiving HAART [10,14,17].

The long-term evaluation of the immune response to the measles vaccine in HIV-infected subjects could provide an insight of the immune response to the measles vaccine. It could also, bring more information about the long-term preservation of measles antibodies among HIV-infected subjects. Furthermore, measles
protective immunity has traditionally been evaluated exclusively in terms of antibody detection, despite data suggesting that cell-mediated immunity is essential in the recovery from measles and for long-term maintenance of immunity [18–20]. The information regarding the cellular immune response to measles vaccination in HIV-infected children and adults is scarce, and the factors associated with primary vaccine failure in HIV-infected individuals are largely unknown.

We conducted this study aiming to prospectively evaluate the short and long-term humoral and cellular immune response to measles vaccine among a group of HIV-infected and non-infected adults. Other objectives of our study were to estimate measles seroprevalence among adults in Mexico and assess the tolerability of measles vaccine among HIV-infected subjects.

2. Methods

2.1. Study setting

In 2004, a massive immunization campaign was undertaken as part of the SIA’s during a measles outbreak in Mexico; 12 million doses of the measles-rubella vaccine were administered to the population 13–39 years of age [21]. According to the estimated HIV prevalence in Mexico, about 12,000 to 48,000 of HIV-infected adults could have been exposed to the measles vaccine [22]. In the HIV/AIDS Clinic of the National Institute of Medical Sciences and Nutrition (INCMNSZ) in Mexico City, about 60% of patients were in the age group targeted during the measles SIA’s in 2004. Considering the lack of information of measles prevalence in this age group in Mexico and the limited information of the safety and efficacy of the measles vaccine in HIV-infected adults, we conducted this study to address these issues.

2.2. Study design

We first conducted a cross-sectional study to determine the prevalence of measles-specific antibodies in a group of HIV-infected and uninfected Mexican adults. Then, individuals that lacked measles-specific antibodies were enrolled for the second phase of the study and were offered the MMR vaccine. Those that agreed to participate were vaccinated and followed for one year after vaccination. Safety and tolerability were clinically assessed, and through CD4+ T-cell count and HIV viral load monitoring at baseline, 2 weeks, 3 and 12 months after vaccination. To evaluate vaccine immunogenicity, measles-specific antibodies and cellular proliferative responses to measles antigens at baseline (i.e. pre-vaccination), 3 and 12 months after vaccination were measured.

The study was approved by the Institutional Review Board of the INCMNSZ and of the Faculty of Medicine of the Autonomous National University of Mexico (UNAM). All subjects gave their written informed consent to participate in the study.

2.3. Study population

HIV-1-infected (HIV-infected) adults of the HIV/AIDS Clinic of the INCMNSZ, who were targeted by the immunization campaign but had not received the vaccine at enrolment, were prospectively recruited between April and July 2004. HIV-uninfected blood donors of the same age group in the INCMNSZ who had not been vaccinated during the campaign served as comparison group. We assessed the measles vaccination status by inquiring subjects whether they had received the vaccine in the ongoing campaign, but no search was done to know previous measles vaccine or wild-type virus infection. Patients who were measles seronegative in the initial survey, that had CD4 T-cell >200 cell/mL, and no contraindication to receive the vaccine; and all measles seronegative controls that agreed to participate, were enrolled for the second part of the study.

2.4. Procedures

To monitor adverse events we applied a structured questionnaire at 2 weeks and 3 months after vaccination. Most common reported adverse events associated to the vaccine, were included in the questionnaire, as well as an open question asking about any other symptoms. To assess possible delayed adverse events we contacted subjects after 12 months. In addition we reviewed all medical charts of measles vaccinated HIV-infected subjects, with particular emphasis in hospitalizations and emergency room visits. HIV-infected patients and controls were also provided with an emergency contact number, which they could call at any time during the follow-up period in the event that any new symptom occurred.

CD4+ T-cell counts were determined by flow cytometry with monoclonal antibodies to CD3, CD4 and CD8 (TruCOUNT, Beckton & Dickinson). HIV-1 RNA levels were determined using an ultrasensitive polymerase chain reaction (AMPLICOR® HIV-1 MONITOR Test, v1.5, Roche) assay.

To estimate the prevalence and assess humoral immune response we measured measles-specific antibodies using a semi-quantitative ELISA (IgG Measles Vidas BioMerieux–Lyon). By manufacturers insert, results are reported as negative, equivocal or positive. If the result was equivocal, a second sample was processed; if the result was again equivocal, it was considered as negative.

A single 0.5 mL dose of the measles—mumps—rubella (MMR) vaccine (Priorix, GlaxoSmith & Kline) containing a lyophilized mixture of 1000 TCID50 live attenuated Schwarz strain, was applied subcutaneously in the deltoid area by a trained health care worker.

To evaluate cellular immune response, peripheral blood mononuclear cells (PBMCs) were separated from a blood sample using the Fycoll-Hypaque gradient. Cells not tested immediately, were stored in liquid nitrogen diluted in bovine fetal serum and DMSO for later use. PBMCs were added to 96-well microtiter plates at a concentration of 3 × 105 per well in RPMI 1640 culture media (Gibco, St. Louis, MO). Measles antigen (Enders strain) prepared from infected Vero cell lysates and uninfected cell controls were added at 1:8, 1:16, and 1:32 dilutions in triplicate wells. After culturing for 5 days, T-cell proliferation was measured by adding (3H)-thymidine (2.5 μCi per well) and incubated for an additional 6–18 h. Phytohemagglutinin (Difco, Detroit, MI) and tetanus toxoid (Calbiochem, La Jolla, CA) were used as positive controls. The antigen-specific stimulation index (SI) was defined as the ratio of the mean counts per minute (cpm) in measles antigen-stimulated wells to the mean cpm in the control wells. Assays with a SI ≥3.0 were considered positive and expressed as mean and standard deviation SI [23–28].

We defined measles seropositivity and seronegativity based on the detection or absence of serum measles IgG. Study subjects whom after vaccination had a positive serum measles IgG were considered seroconvertors. Vaccine failure was defined as the absence of serum measles IgG 3 months after vaccination. Secondary vaccine failures occurred among those who had seroconverted, but at the 12 months evaluation had a negative serum measles IgG. A positive cellular proliferative response to measles antigens was considered if the SI was higher of equal to 3.0. Adaptive immune response was defined as either positive IgG measles ELISA, positive cellular proliferative response after vaccination, or both [11].

2.5. Statistical analysis

Sample size was calculated assuming a 90% and 30% seroconversion in HIV non-infected and HIV-infected subjects respectively.
Table 1
Baseline characteristics of MMR vaccinees and changes in CD4+ cells and viral load during follow-up.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>HIV– n = 22</th>
<th>HIV+ n = 26</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years (mean ±SD)</td>
<td>24.8 ± 4.8</td>
<td>30.8 ± 5.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>17 (77%)</td>
<td>23 (88.5%)</td>
<td>0.07</td>
</tr>
<tr>
<td>CD4+ cell/mL (mean ± SD)</td>
<td>496.81 ± 179.8</td>
<td>456.1 ± 193.7</td>
<td>0.159</td>
</tr>
<tr>
<td>HAART n (%)</td>
<td>22 (84.6%)</td>
<td>23 (88.5%)</td>
<td>0.191</td>
</tr>
<tr>
<td>UndetectableVL n (%)^a</td>
<td>–</td>
<td>17 (74%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Indeterminate measles IgG antibodies n (%)^b</td>
<td>3 (14%)</td>
<td>6 (23%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

^a Proportion of patients that had an undetectable HIV RNA (<50 copies/mL).

^b By manufacturers instructions, a lecture of 0.5–0.7 is interpreted as equivocal, and for purposes of the subjects with repeated equivocal results were classified as lacking measles antibodies.

We estimated that 10 subjects per group would be necessary to detect a 60% difference with an 80% power and a one sided 0.05 α error, accounting for 20% losses to follow-up. We estimated that assuming a 95% measles seroprevalence in the general population, we needed to test 200 subjects in each group to find 10 measles IgG(−) subjects. We also calculated that with 400 subjects we could estimate a 99% confidence interval for a true prevalence of 0.9 ± 0.1. Prevalence was estimated using simple proportions. To compare differences in the immune response to the vaccine among HIV-infected and uninfected subjects we used χ² and Fisher’s exact tests. Continuous parametric variables were compared using Student’s t test. The Mann–Whitney U test was used for non-parametric variables. CD4+ T-cell counts and HIV viral load at baseline and follow-up were compared using the Friedman test for repeated measures. Statistical significance was defined as p < 0.05. Statistical analysis was performed by using SPSS software (version 15.0; SPSS).

3. Results

A total of 379 adults were enrolled, 160 HIV-infected patients and 219 controls. Sample size was not met for HIV-infected patients because we had already tested all available eligible patients in our clinic. HIV-infected patients were predominantly male (131 (81.9%) vs. 147 (67.1%) p = 0.0001), and slightly older (32.3, SD ± 5.0 vs. 28, SD ± 6.7 years; p = 0.01) in comparison to the HIV non-infected group. The majority of HIV-infected patients (95%) were receiving highly active antiretroviral therapy (HAART) and had a median CD4+ T-cell count of 349 cells/mL (IQR, 231–513 cells/mL). Measles seroprevalence was 78.36% (95% CI, 74–83%). The proportion of HIV-infected and non-infected patients with measles antibodies was 76.2% (95% CI, 69.5–82.9%) and 80% (95% CI, 74.5–85.2%) respectively (p = 0.39). Of the total measles seronegative individuals, 26 HIV-infected patients and 22 controls agreed and/or were eligible (CD4+ >200 cell/mL) to receive the vaccine. Characteristics of vaccinees at baseline and follow-up are described in Table 1. One HIV-negative individual was lost to follow-up after 3 months evaluation.

3.1. Adverse effects

Only one patient (3.8%) in the HIV-infected group reported a self-limited rash and fever at day 10 post-vaccination. No adverse events were reported at one year of follow-up neither during interviews with HIV-infected patients nor in the chart review. No adverse effects were seen in the comparison group. We found no differences in the mean CD4+ T-cell count (P = 0.159) or mean viral load (P = 0.191) before and after vaccination in the HIV-infected group; however, in one patient the viral load increased temporarily from <50 copies/mL to 115 copies/mL on day 15 post-vaccination, decreasing to <50 copies/mL at the 3 and 12 months evaluation.

3.2. Immune response to the MMR vaccine

1. Humoral immune response: By study criteria, all vaccinees were measles seronegative at baseline. At 3 months post-vaccination, we found no statistically significant differences in the proportion of seroconvertors between both groups: 81% in the HIV-infected and 86% in the HIV non-infected (P = 0.71) (Fig. 1). Conversely, secondary vaccine failure at one year were noticeably different, with only 34% remaining measles seropositive among HIV-infected and 80% in the controls (P = 0.002).

2. Cellular immune response: Despite measles seronegativity at baseline, 30.4% of HIV-infected patients and 54.5% (P = 0.01) HIV non-infected, had a positive cellular proliferative response (measles SI ≥ 3) (Fig. 1). The mean SI (±SD) was 2.4 ± 0.4 in the HIV-infected group and a 4.3 ± 0.8 in the HIV non-infected (P = 0.018). At 3 months post-vaccination the proportion of HIV-infected and HIV non-infected subjects with a measles SI ≥ 3 was 48% and 50%, respectively (P = 0.89); similarly there were no significant differences in their mean SI 5.3 ± 1.4 and 3.75 ± 0.6 (P = 0.79). At the one year evaluation, the proportion of subjects with a positive cellular proliferative response was 69.2% in the HIV-infected group and again not different from the control group 57.1% (P = 0.39) Their mean SI were also comparable (5.5 ± 0.9 vs. 4.7 ± 0.7) (P = 0.7).

Fig. 1. Percentage of HIV-infected and uninfected individuals with a humoral and cellular immune response to the MMR vaccine at baseline (pre-vaccination), and at 3 and 12 months after vaccination.
3. Adaptive immune response: When considering both humoral and cellular immune responses, the proportion of individuals with a positive adaptive immune response at baseline, 3 and 12 months, were similar in both the HIV-infected and the control group (Fig. 2).

We sought to identify risk factors which could have an impact on the frequency of positive cellular proliferative response vs. no cellular proliferation to measles antigens, among the HIV-infected patients, at baseline, 3 and 12 months. We also sought to identify factors which could have been associated to a positive humoral immune response at 3 and 12 months after vaccination. We compared variables such as sex, age, use of HAART, CD4+ T-cell count at baseline, at the time of HIV diagnosis, nadir of CD4+ T-cell count, baseline HIV viral load, baseline SI, and change in SI at 3 months and found no significant differences neither between vaccine responders and non-responders, nor between those with and without secondary vaccine failure (data not shown).

4. Discussion

The main objective of our study was to evaluate the short- and long-term humoral and cellular immune response to measles vaccination among HIV-infected subjects. We observed a high rate of seroconversion to measles among MMR vaccinated HIV-infected adults, and not statistically different to a group of HIV non-infected adults used as comparison group. However, most HIV-infected adults experienced a rapid decline in measles antibody titres. This happened despite an adequate immune reconstitution with HAART and a preserved cellular immune response against measles antigens. Similar finding were recently observed in a prospective study of HIV-infected children not receiving ART, immunized with an MMR vaccine in Zambia. The initial humoral immune response among HIV-positive children was comparable to that in HIV-negative (88% vs. 94%). The authors also observed a faster waning of measles-specific antibody titres among HIV-infected children at 27 months of follow-up - 43% vs. 89% seropositivity in HIV-positive and negative children respectively [10]. Bekker et al. found similar rate of loss of measles antibodies in a cohort of HIV-infected children immunized before starting HAART despite the increase in B cells and the normalization of lymphoproliferative T-cell responses when children were subsequently started on HAART [29]. Previous and recent cross-sectional studies are consistent with these observations [14,30].

The present study contributes with new information about the immune response to measles vaccine among HIV-infected patients by demonstrating that the immune reconstitution achieved with the use of HAART does not prevent the high rate of secondary vaccine failure previously observed among HIV-infected patients not receiving treatment. There is no clear explanation to this phenomenon, which has been observed also for influenza, Streptococcus Pneumoniae and other antigens independently of the CD4+ T-cell count or antiretroviral use [31–33]. A possible mechanism for early antibody loss among HIV-infected individuals may be found on recent studies, where HIV-1 infection has been observed to induce polyclonal B cell activation and apoptosis as early as 17 days after the primary infection [34,35]. Additionally, polyclonal B cell activation, B cell exhaustion, and a decreased number and responsiveness of memory B cells persist during HIV chronic infection [34,36,37]. Furthermore, HIV-induced B cell functional abnormalities are not restored with effective HAART [38,39] even when the absolute number of B cells increase with therapy [29,40]. A persistent dysfunction of memory B cells despite the presence of effective ART could explain the lack of long-term maintenance of measles antibodies in our group of HIV-infected adults that achieved an apparently adequate immune reconstitution with the use of HAART.

A relevant observation in our results is the initially high seroconversion rate, which is amongst the highest reported for HIV-infected patients. Previous studies evaluating humoral response to measles vaccine among HIV-infected children have shown divergent results, although most of these studies were conducted in children not receiving HAART and followed for short periods of time. The factors previously associated with a good humoral response to measles vaccine are younger age at vaccination, high CD4+ cell counts, and use of antiretroviral treatment suggesting that a preserved immune status is essential for an initial adequate response to vaccination in children [4,5,7,13,14]. We did not found any association between HIV-infected patient characteristics and a positive humoral or cellular immune response at 3 or 12 months after vaccination, however the study lacks statistical power to conclude confidently the lack of association between the factors we sought at and a positive immune response. Bearing this limitation in mind, we speculate that the relatively high CD4+ cell count (mean 496 cells/mL) at the time of immunization was an important factor in the initial strong humoral immune response in our cohort of patients.

In addition, another important factor that could have influencd our results is the unoberved proportion of subjects that may have had received the measles vaccine in infancy or in previous SIA’s. The subjects included in this study, if previously vaccinated may had low, though non-detectable antibody titres at baseline. If this is the case, we would have been observing the response to re-immunization, rather than the primary immune response to the vaccine in a subset of our subjects. This hypothesis is supported by two facts: a high proportion of subjects in both groups had a positive SI at baseline, and also a considerable proportion in each group had indeterminate measles antibodies at baseline (see Table 1). Measles seroconversion after re-immunization in HIV-infected children receiving HAART that had primary vaccine failure varies between 64% and 90% [14,15,41–44]. Although we cannot differentiate which subjects were re-immunized, we consider that this would not change the main conclusions of our study. This is so, because the proportion of subjects with positive cellular response and indeterminate antibodies at baseline is not different between groups, which allow us to infer that the proportion of re-immunized subjects is equally distributed among HIV-infected and non-infected subjects. The duration of follow-up in previous studies has not been long enough to know whether the humoral immune response after re-immunization would be long-lasting.

In addition, we may have also introduced bias by regarding patients with indeterminate measles serology as being negative, since it is more likely that these patients have had low measles antibody titres. We did so, because we considered that it would be better for them to receive the vaccine in case they were truly negative and susceptible to infection by the wild-type virus. Thus,
these subjects were more likely to have been re-immunized and had a higher probability of a good humoral response than those previously unexposed to measles antigens. Nonetheless, we consider that this issue is applicable to both HIV-infected and uninfected subjects, and would not change the main conclusions of the study.

Data regarding the efficacy of the measles vaccine in HIV-infected adults is scarce. The only two studies that have evaluated the measles vaccine in HIV-infected adults were conducted before the HAART era. Wallace et al. vaccinated six HIV-infected adults of whom only two patients seroconverted; both remaining seropositive for measles at one year of follow-up [17]. In another study, three HIV-infected adults with no detectable measles antibodies were vaccinated, and none developed measles-specific antibodies [45]. In neither one of these studies the proportion of re-immunized subjects was known.

Another important feature of our study is the evaluation of the cellular proliferative responses to measles antigens after measles immunization as a measurement of cellular immune response. Although, there is evidence that cell-mediated immunity is important in the protection against measles [20,46], most evaluations of the vaccine efficacy have been established in terms of the development of measles-specific antibodies. To our knowledge this is the first study to evaluate the cellular immune response to the measles vaccine in HIV-infected adults. The results of our study are in accordance with four other reports of proliferative cellular responses to measles antigens among vaccinated HIV non-infected subjects. About 50–80% of vaccinees had a SI ≥ 3, regardless of the time elapsed after vaccination and measles antibodies titre [24,26,47,48]. In all these studies the percentage of positive lymphoproliferative responses after vaccination were independent of the number of vaccine doses, antibody titres, and time after vaccination [47,48]. Nonetheless it is important to address that even when the observed proportion of HIV-infected individuals with SI ≥ 3 is similar to that of healthy subjects in previous studies, and this response was not statistically different from the comparison group in our study, the proliferative immune responses among HIV-infected individuals receiving HAART do not necessarily correlate with improved cellular functionality even when complete viral suppression and adequate CD4+ T-cell count reconstitution has been achieved [49]. Therefore, further studies to determine to what extent the cellular immune response in absence of detectable measles antibodies confers protection are needed. In addition, our analysis of cellular proliferative responses lacks detailed cellular phenotypification, which is a limitation of the study.

Other objectives of our study were to assess the tolerability of measles vaccine among HIV-infected adults, and to estimate measles seroprevalence among adults in Mexico. We observed one self-limited mild adverse event in the HIV-infected group. This is consistent with the 5–10% of healthy children presenting with fever, rash, myalgia and/or arthralgia on the first 10 days after measles vaccination [50]. No significant changes in CD4+ T-cell counts or HIV viral load were observed. During the one year of follow-up there were no severe adverse events related to the vaccine use in either the HIV-infected or the control group. Our findings concur with the report of the Measles Elimination Goal campaign in the South African countries [12], and with studies done in HIV-infected children and adults [45], where the measles vaccine was found to be safe. The only fatal case documented to be a consequence of measles vaccine application in an HIV-infected individual, appears to be related to the severe immunocompromise of the patient at the time of vaccination [51].

Finally, we found that the prevalence of subjects with measles-specific antibodies among this group of adults in Mexico was 78.36% (95% CI, 74–83%). Moreover, the prevalence was not different between HIV-infected (76%) and HIV-uninfected (80%). Similar measles prevalence (76%) was found in a serologic surveillance study of 406 high-school and college students 14–24 years old during the same period in Mexico City [52]. The observed prevalence was lower than expected, since we erroneously assumed 95% IgG anti-measles prevalence for this population considering the high vaccine coverage for children younger than five years of age reached in 1992 and thereafter. However, the results of both studies are in accordance with the measles vaccine coverage achieved between 1970 and 1992, a period during which the measles vaccine was slowly introduced in Mexico, resulting in a partially immunized population who was 13–35 years old in 2004 [21,53] making this population susceptible to the more recent outbreaks [54]. Also, our results are consistent with previous studies in which measles seroprevalence among HIV-infected subjects have been found to be the same as in the general population [17,55–57]. Moreover, we may have underestimated measles antibody prevalence, because the ELISA used in this study may have a slightly lower sensitivity to detect antibodies when compared with the plaque reduction assay to detect neutralizing antibodies, particularly at low titres [58].

In conclusion, our study provides evidence that HIV-infected adults without severe immunocompromise have an initial antibody response that is not different to HIV non-infected subjects yet; in the HIV-infected adults this response is transient and after one year disappears in most individuals, despite an adequate immune reconstitution due to HAART. No significant toxicity occurred in HIV-infected vaccinated subjects, thus we consider that HIV-infected young adults can and should be included in immunization supplementary activities when needed, if measles control is to be achieved. Additionally, the administration of measles vaccine in this group before travelling to endemic areas is likely to be safe and effective at least for a short period of time. In addition, we observed that HIV-infected individuals exhibit a cellular immune response that appears to be comparable to that of healthy individuals. Further study of the duration of immunity and efficacy of B and T-cell immunity in HIV-infected adults and children could provide new insights for the understanding of primary and secondary measles vaccine failures, and to know to what extent the cell-mediated immunity is protective against disease.

Acknowledgments

We thank the patients from the HIV/AIDS Clinic of the Department of Infectious Diseases and blood donors from the Blood Bank who generously and enthusiastically participated in the study. We thank Cynthia Carrillo, Alicia Piñeira, Rafael Baizabal, Gabriela Montejano, Melissa Hernandez and Norma Lopez for recruiting patients and for sample collection and transport; and Dr. Beatriz R. Ruiz-Palacios for critical review of the manuscript. We thank Dr William Moss who generously reviewed and commented the manuscript.

Financial Support: This work was supported in part by a grant from the Fogarty International Center and the Office of Research on Women's Health (TW006193) and partially Infectious Diseases Department of the INCMNSZ and the Infectious Diseases Department HIV/AIDS Clinic from the INCMNSZ.

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