Broadly neutralizing antibody specificities detected in the genital tract of HIV-1 infected women

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Background: Broadly neutralizing antibodies (bNAbs) targeting conserved epitopes on the HIV envelope glycoprotein have been identified in blood from HIV-1 infected women. We investigated whether antibodies in the genital tract from these women share similar epitope specificities and functional profiles as those in blood.

Methods: Immunoglobulin (Ig)G and IgA antibodies were isolated from cervicovaginal lavages or Softcups from 13 HIV-infected women in the CAPRISA cohort using Protein G and Peptide M, respectively. Binding antibodies to envelope antigens were quantified by ELISA and binding antibody multiplex assay. Neutralizing antibody titers and epitope targets were measured using the TZM-bl assay with Env-pseudotyped wild-type and mutated viruses.

Results: HIV-specific IgG, but not IgA, was detected in genital secretions and the ratio of total IgG to HIV-specific IgG was similar to plasma. HIV-specific IgG reacted with multiple envelope antigens, including V1V2, gp120, gp140 and gp41. Two women had high plasma titers of HIV-specific IgG3 which was also detected in their genital tract samples. IgG from the genital tract had neutralizing activity against both Tier 1 and Tier 2 primary HIV-isolates. Antibodies targeting well known glycan epitopes and the membrane proximal region of gp41 were detected in genital secretions, and matched specificities in plasma.

Conclusions: Women with plasma bNAbs have overlapping specificities in their genital secretions, indicating that these predominantly IgG isotype antibodies may transudate from blood to the genital tract. These data provide evidence that induction of systemic HIV-specific bNAbs can lead to antiviral immunity at the portal of entry.

Introduction

Sexual transmission of HIV remains the most common route of infection, with young women especially at risk [1,2]. Mucosal surfaces of the genital tract are the principal and initial sites of infection, and therefore local mucosal antibody immunity is crucial in the control of HIV replication before systemic dissemination [3]. Broadly

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neutralizing antibodies (bNAbs) are able to inhibit the majority of HIV strains and, if elicited by an HIV vaccine, are likely to be effective at blocking infection at the site of entry. In non-human primates, passively infused bNAbs have been shown to inhibit simian-human immunodeficiency virus infection using the high-dose vaginal challenge model [4−7]. In addition, vaginally applied bNAbs protected macaques from simian-human immunodeficiency virus vaginal challenge [8,9]. An HIV vaccine may therefore be required to elicit potent, long-lasting HIV-specific antibodies in blood and at the genital mucosa, where the virus is first encountered. In the RV144 human vaccine trial that showed moderate efficacy, HIV-specific V1V2 binding antibodies, particularly of the IgG3 subclass, were found to correlate with a reduced risk of HIV infection [10−12]. However, as no mucosal sampling was done in this vaccine trial, the presence of these potentially protective antibodies in the genital tract could not be assessed.

HIV-specific binding and neutralizing antibodies have been described in the genital tract of HIV-infected women [13−15], and in highly exposed, but persistently HIV seronegative women [16−18]. HIV-specific antibodies from lower genital tract secretions have been shown to be predominantly IgG rather than IgA, suggesting that transudation of systemic HIV-specific IgG antibodies contributes to IgG dominance at this mucosal surface [13,19−21]. The neonatal receptor (FcRn) is involved in IgG transport across polarised epithelial cells lining mucosal surfaces such as the single-layered columnar epithelial cells of the endocervical canal, in a pH-dependent manner [22]. B cells have also been identified in tissue from the genital tract of HIV-infected women [23−25], suggesting that there is potentially also local production of antibodies from resident B cells in addition to transudation of antibodies from blood.

Natural HIV infection studies have shown that a proportion of HIV-infected individuals develop bNAbs in their plasma, generally after many years of infection [26−30]. The targets of these bNAbs on the HIV envelope have been mapped to the CD4bs, the glycan at 332, the V1V2 domain, the membrane proximal external (MPER) region, and the gp120-gp41 interface [31,32]. Approximately 20% of HIV-infected individuals in the CAPRISA 002 cohort developed plasma bNAbs after 2−4 years of infection [27]. In this study, we investigated whether HIV-specific bNAbs are present in genital secretions from these HIV-infected women who developed breadth systemically, and whether these antibodies recognized common binding and neutralization epitopes.

Methods

Study participants
Plasma and genital secretions collected by cervicovaginal lavages (CVLs) and/or Softcups were obtained from 13 women in the CAPRISA 002 and CAPRISA 004 cohorts, from Kwa-Zulu Natal, South Africa [33−35] (Supplementary Table 1, http://links.lww.com/QAD/A883). This study was approved by the Human Research Ethics Committees of the University of Witwatersrand, University of KwaZulu-Natal and University of Cape Town. All participants provided written informed consent.

Collection of genital secretions
CVL samples were collected as previously described [36]. Each woman underwent a speculum examination during which her cervix was irrigated with a lavage of 10 ml sterile saline. Aspirated saline was transferred to a clean 15 ml tube and centrifuged at 2300 rpm for 10 min to remove cells. Supernatants were harvested and stored at −80°C. In addition, cervical secretions were collected using a Softcup Menstrual cup (EuroFemPro, the Netherlands) and processed as previously described with modifications [37]. For this, the Softcup was inserted into the vagina for a minimum of 1 h by a clinician, placed into a 50 ml tube and centrifuged [38]. The fluid phase was collected into an eppendorf tube and the volume measured. The pellet was resuspended and centrifuged in 300 μl PBS to increase antibody recovery and the fluid phases combined to a total volume of 500 μl. This was used for IgG purification on the same day.

Immunoglobulin isolation and quantification
IgG antibodies were isolated using Protein G (Pierce/Thermo Scientific), whereas IgA was isolated by Peptide M (InvivoGen) as previously described [39]. The final fractions were concentrated using 50 000 MW concentrators (Millipore). Total IgG and IgA concentrations in plasma, CVLs and Softcup secretions were quantitated by ELISA, as previously described [40]. High protein-binding 96-well microplates (Nalge Nunc International, Rochester, New York, USA) were coated with 4 μg/ml goat polyclonal antihuman IgA or IgG (Jackson ImmunoResearch Laboratories, West Grove, Pennsylvania, USA), and then blocked with 5% goat serum in PBS-0.05% Tween 20. Duplicates of two-fold serially diluted samples and a human Immunoglobulin (Ig) reference serum (Human Immunoglobulin Calibrator; Binding Site, Birmingham, UK) were added to the plates and incubated for 1 h at 37°C. The captured Ig was detected after consecutive incubations with biotin-labelled goat F(ab')2 specific for human IgA or IgG (BioSource, Camarillo, California, USA) and horseradish (HRP)-labelled avidin (Sigma, St. Louis, Missouri, USA). The ELISA was developed with TMB substrate (Thermo Fisher Scientific, Rockford, Illinois, USA) and stopped with a 1 M H_2SO_4 solution. The plates were read at 450 nm on a microplate reader (Molecular Devices, Sunnyvale, California, USA). A standard curve was run on each plate with serial dilutions of a commercial human IgG (Sigma-Aldrich) or IgA (Jackson Immunoresearch, Pennsylvania, USA) to calculate antibody concentrations.

Binding antibody multiplex assay

Binding antibodies to HIV proteins and peptides were measured using a customized HIV binding antibody multiplex assay (BAMA), as previously described [10,41]. The HIV antigens used included: consensus gp120 Env (Con6 gp120), clade C gp140 Env trimer (1086 Trimer), clade C TV1 gp140, Group M consensus gp140 Env (ConS gp140), clade B gp70 V1V2 fusion protein (gp70_V1V2), a clade C V1V2 fusion protein (1086_V1V2), clade B MPER tetramer (MPR.03) and gp41 (Immunodiagnostics, Woburn, Massachusetts, USA). Carboxylated fluorescent beads (Luminex Corp., Austin, Texas, USA) were covalently coupled to purified HIV antigens and incubated with clinical samples at various dilutions. CVL supernatants (not purified for IgG) were used at a 1:5 dilution, whereas plasma antibodies were measured from a titrated dilution (1:100 to 1:312 500). HIV-specific total IgG and IgG3 were detected using PE-conjugated mouse antihuman IgG and IgG3 (both Southern Biotech, Birmingham, Alabama, USA), respectively. The beads were washed and acquired on a Bio-Plex instrument (Bio-Rad) and results expressed as mean fluorescence intensity (MFI). Responders had MFI 100 or more. The specific activity (MFI*dilution/ antibody concentration) was calculated for genital tract IgG binding to account for variability in antibody levels recovered from different women. Responders had specific activity more than 0.01.

HIV neutralization assays

Neutralization was measured using HIV-Env pseudo-typed viruses in the TZM-bl assay. Envelope genes were either cloned previously in our laboratory [42] or obtained from the NIH AIDS Research and Reference Reagent Program. This included one Tier 1 virus (SF162.LS) and three Tier 2 viruses (ConC, CAP45.G3 and TRO.11). Murine leukaemia virus was included in the assay as a negative control. Neutralization was measured as a reduction in luciferase gene expression after a single round of infection in JC53bl-13 cells, also known as TZM-bl cells, with Env-pseudotyped viruses [43]. IC_{50} was calculated as the IgG concentration causing a 50% reduction of relative light units.

Epitope mapping

For epitope mapping via ELISA, plates were coated with ConC gp120 proteins or with an MPER peptide (MPR.03). The ELISA was performed using purified IgG, as described above. Antibody binding to wild-type gp120 but not mutant gp120 (containing an N332A mutation), indicated dependence on the glycan at position 332. Direct antibody binding to the MPR.03 peptide was used to demonstrate the presence of MPER-specific IgG. For mapping via neutralization, viruses containing mutations at key epitopes were used in the neutralization assay, described earlier. This included ConC N160A, CAP45.G3 K169E and TRO.11 N332A mutants, used to map bNAb epitopes targeting sites in the V2 and V3 regions, shown using monoclonal antibodies targeting these sites (data not shown). A reduction in IC_{50} of the mutant virus compared with the wild-type virus was used to identify the epitope specificities of the isolated IgGs.

Statistical analysis

The Mann–Whitney test was used for independent sample comparisons and a Wilcoxon matched-pairs signed rank test was performed for dependent sample comparisons, using GraphPad Prism version 5.0 (Graph-Pad Software, La Jolla, California, USA). All tests were two-tailed and *P* values of less than 0.05 were considered significant.

Results

Higher concentrations of IgG than IgA isotypes in genital secretions

The quantity of total IgG and IgA antibodies isolated from matched plasma and genital samples of women, previously identified as having plasma bNAbs, was investigated. CVL samples were initially obtained from seven antiretroviral therapy (ART)-naive women in the CAPRISA 002 cohort at 3 years postinfection [24]. The concentration of total IgA was negligible in genital secretions with a mean value of less than 1 μg/ml, whereas in plasma the mean value was 359 μg/ml. Overall, IgG concentrations were 2 logs greater and significantly higher than IgA concentrations in both plasma (*P* = 0.016) and CVL (*P* = 0.016) (Fig. 1a).

To determine whether these antibodies were HIV-specific, we tested them in a gp120 ELISA (Fig. 1b). CVL IgG antibodies bound gp120 at a median titer of 1:34, whereas the plasma HIV-specific IgG binding titer was 3 logs higher at 1:53 697. HIV-specific IgA antibodies in plasma were detected at a median titer of 1:266. None of the individuals had HIV-specific IgA detected in CVL, with binding titers at the same level as background. Given this, we focused the rest of the study on IgG antibodies. In order to accurately compare HIV-specific IgG concentrations in plasma and CVL, we calculated the ratio of HIV-specific to total IgG. Even though plasma consistently had higher titers of IgG than CVL, the median HIV-specific activity was similar in CVL and plasma (Fig. 1c).

In order to optimize sample collection for neutralizing antibody assays, we explored the use of the Softcup for collecting genital secretions. As this method requires fresh sample processing, we recruited four of the women with bNAbs from the CAPRISA 002 cohort who were by that time on ART, but still had detectable neutralization titers (Mkhize, unpublished data) along with an additional six chronically HIV-infected women from the CAPRISA 004 cohort who also developed plasma bNAbs
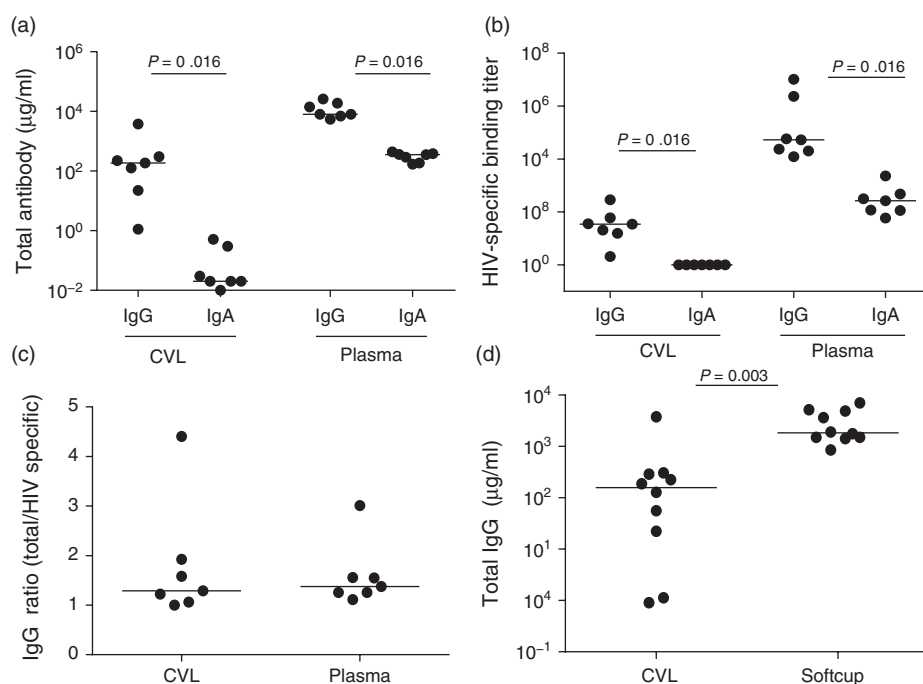
Fig. 1. Detection of total and HIV-specific immunoglobulins in the female genital tract. (a) Quantification of immunoglobulin (Ig)G and IgA concentrations in cervicovaginal lavage (CVL) and plasma of 7 CAPRISA 002 women with broadly neutralizing activity. (b) gp120-specific binding of IgG and IgA antibodies purified from CVL and plasma. (c) Ratio of total IgG to HIV-specific IgG concentrations in CVL and plasma from the 7 CAPRISA 002 women, based on 17b mAb standard curve for gp120 IgG. (d) Comparison of total IgG yields from CVL (from CAPRISA 002) and genital secretions collected using Softcup from 10 women in the CAPRISA 002 and 004 cohorts.

(Madzivhandila, unpublished data). We compared the yields of total IgG obtained from CVL to those recovered from the genital tract via the Softcup in all 10 women. The total IgG recovered from CVL varied amongst the participants with a range of $0.9-3773\,\mu g/ml$, whereas the total IgG collected via Softcup was more consistent with a range of $1060-6752\,\mu g/ml$ (Fig. 1d). Compared with CVL, the Softcup method resulted in a 13-fold higher level of total IgG ($P=0.003$).

HIV-specific antibodies in cervicovaginal lavage recognize multiple HIV envelope antigens

The kinetics, magnitude, and specificities of antibodies in CVL and plasma collected from women at 1, 2 and 3 years postinfection were compared using BAMA. HIV-specific IgG binding reactivity to all eight HIV Env antigens was detected in CVLs and plasma, and as there was little difference between time points, the data were analysed together (Fig. 2). Antibodies to gp120, gp140, gp41 and MPER were present at all time points at similar levels in CVL and plasma. Only antibodies to the V1V2 antigens differed, with genital tract IgG binding levels significantly lower than plasma [1086_V1V2 ($P=0.0001$); gp70_V1V2 ($P=0.0002$)]. IgG responses to gp70_V1V2 were better than to 1086_V1V2 and these were detected in four of seven women at 1 or more time points. Overall, these data suggest that HIV-specific IgG antibody specificities in the genital compartment generally match

those found in blood plasma, even though levels were lower in the genital compartment.

Considering the important role of the IgG3 subclass in HIV-1 vaccine studies [10,11] and bNAbs [44,45], we further examined this subclass binding response in the genital compartment. Two individuals, CAP256 and CAP177, were found to have detectable HIV-specific IgG3 responses in both plasma and genital compartments (Fig. 3). For CAP256, plasma IgG3 antibodies to all antigens remained at high titers over time although responses to gp70_V1V2 decayed slightly by 3 years postinfection. Declining responses to all antigens were also observed in CVL although V1V2 IgG3 responses were not detected at any time-point. Plasma from CAP177 contained HIV-specific IgG3 to all antigens except gp70_V1V2. In this individual, low titers of these antibodies were also found in the CVL at 1 year postinfection but declined to below the levels of detection at later time points. This is likely because of the low overall concentrations of IgG antibodies recovered from this participant at the 2- and 3-year time points (not shown).

HIV-specific neutralizing antibody activity in the female genital tract

Next, we determined whether HIV-specific antibodies in CVLs had neutralizing activity. All seven HIV-infected
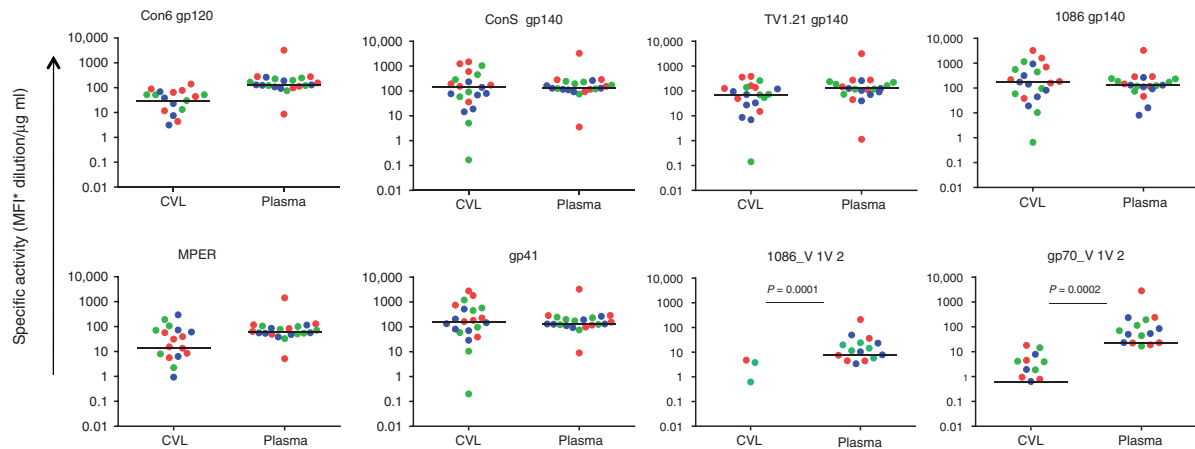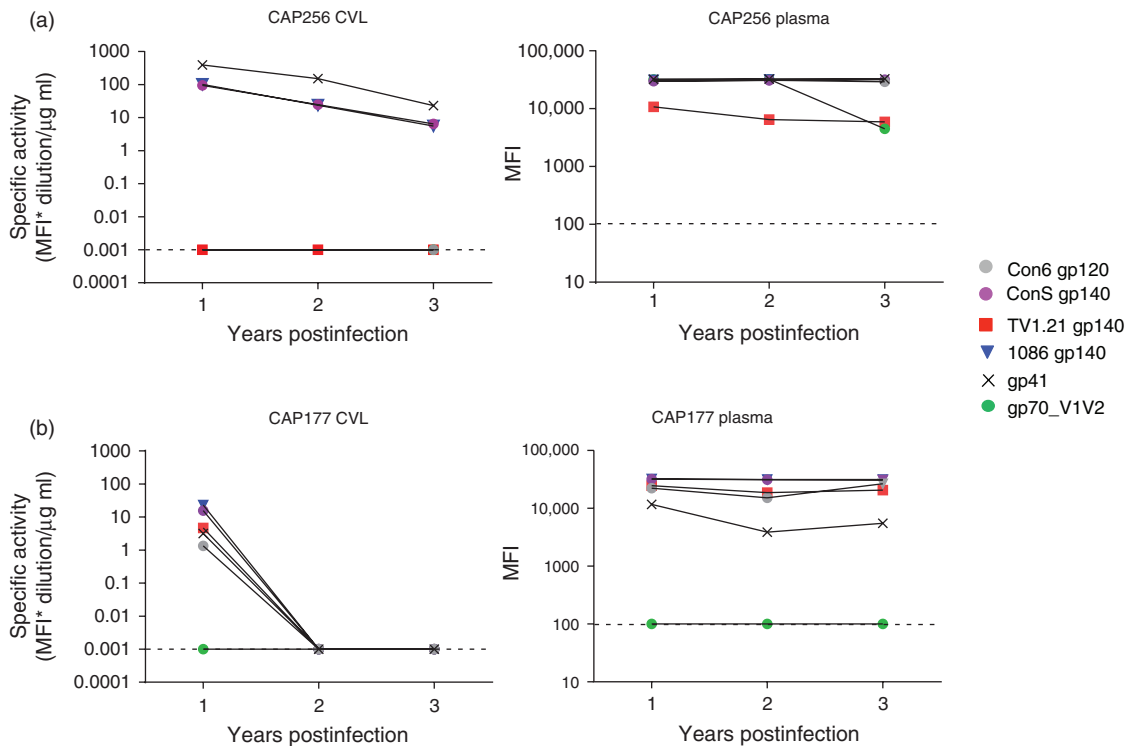
Fig. 2. HIV-specific activity of immunoglobulin (Ig)G antibodies in cervicovaginal lavage (CVL) and plasma. IgG-binding antibodies were measured in CVL and plasma from the 7 CAPRISA 002 women who developed broadly neutralizing antibodies. Dots represent CVL and plasma samples from 1 year (red), 2 years (green) and 3 years (blue) post-HIV infection. Reactivity to eight antigens was evaluated via the HIV-1 BAMA. The median fluorescence intensity (MFI) values were normalized to total IgG concentration (specific activity). Samples that had MF1 less than 100 were considered nonresponders and had no values for specific activity, therefore the points are not reflected on the plots. Responders had a specific activity more than 0.01 for all antigens.

women previously shown to have bNAbs [27] had HIV-specific IgG antibodies that neutralized SF162, an easy-to-neutralize Tier 1 virus (Fig. 4a). Furthermore, they also all showed dose–dependent activity against ConC, a Tier 2 virus, although this did not reach 50% neutralization in three of seven women. The potent neutralization of the more sensitive SF162 suggested that

Tier 1 neutralizing antibodies were more prevalent in CVL, as is also seen in plasma. However, there was a wide range in IC$_{50}$ values among these samples with CAP8 showing the highest level of activity against both viruses.

As antibody concentrations were generally low in CVLs, we next tested IgG antibodies freshly collected from these

Fig. 3. Immunoglobulin (Ig)G3 binding to HIV-specific antigens. IgG3 responses were measured against Env antigens at 1, 2 and 3 years post-HIV infection. Responses were detected in CAP256 (a) and CAP177 (b), represented as specific activity for cervicovaginal lavage (left panel) and MFI for plasma samples (right panel).
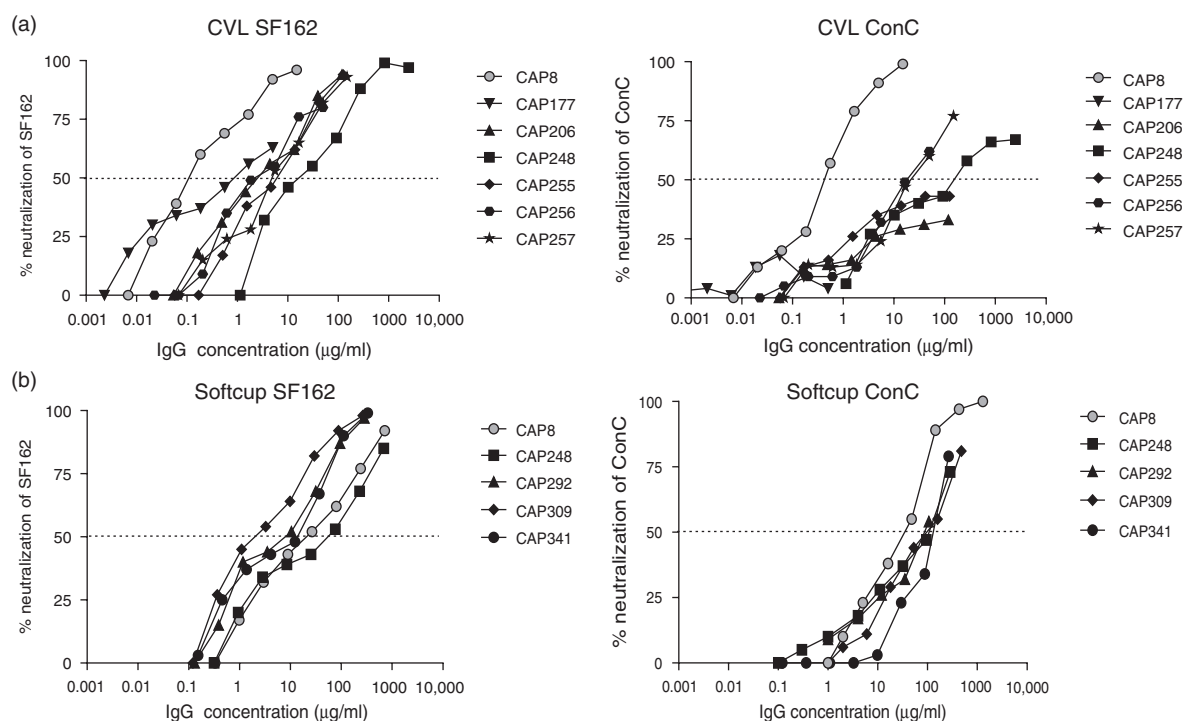
Fig. 4. Neutralization of HIV by purified immunoglobulin (Ig)G from the genital tract. SF162 (Tier 1) and ConC (Tier 2) viruses were tested in a TZM-bl neutralization assay using IgG isolated from cervicovaginal lavage supernatant (a) and Softcup (b) from women in the CAPRISA 002 and 004 cohorts. The dotted line represents the IC_{50}.

women using cervical Softcups to improve IgG recovery [38] and allow for more neutralization assays to be performed (Supplementary Table 1, http://links.lww.com/QAD/A883). This included two CAPRISA 002 women (CAP8 and CAP248) who were receiving ART at the time of Softcup sampling, as well as three additional women from the CAPRISA 004 cohort who were ART-naive. Softcup-derived IgGs isolated from five of these women were able to neutralize both SF162 and ConC (Fig. 4b). In particular, the ability of all samples to neutralize ConC with measurable IC_{50} titers was a notable improvement over the CVL preparations. This is despite the fact that some of these women were on ART that is known to reduce antibody titers [46–48]. Overall, the IC_{50} values of the curves suggested that IgG recovered from the Softcup provided a more consistent preparation compared with CVL.

Mapping of genital tract IgG antibody specificities

We previously showed that the plasma bNAbs in CAP177 were dependent on the glycan at position 332 in the V3 region of gp120 [27]. To determine whether genital tract antibodies shared the same specificity, we used a wild-type gp120 and an N332A mutant protein that lacked this glycan, in an ELISA assay. PGT128, a mAb that is highly dependent on N332 [49] showed significantly less binding to this mutant protein (data not shown). Comparison of IgG binding levels revealed a four-fold

reduction in binding to the mutant protein by IgG from CVL and a three-fold reduction for plasma IgG (Fig. 5a). This indicated that a subset of antibodies isolated from the CVL of CAP177 targeted the N332 glycan epitope on gp120 similar to the plasma antibodies.

Plasma bNAbs in CAP206 were previously shown to target the MPER of gp41 and bind the MPR.03 peptide in an ELISA assay [45,50]. We found that IgG antibodies isolated from both plasma and CVL of CAP206 bound the MPR.03 peptide with comparable levels (Fig. 5a) indicating that antibodies with a similar specificity were present in both compartments.

We next mapped antibodies by neutralization assay using epitope-ablating mutants. For this we used the more abundant IgG collected via Softcup which allowed us to test multiple mutants (Fig. 5b). For CAP8, purified IgG antibodies from cervical Softcups and plasma were sensitive to the N160A mutation in ConC that is characteristic of many V2-dependent antibodies [51,52]. A V2 antibody was previously isolated from blood of donor CAP256 that is sensitive to the K169E mutation [53]. Here we show IgG antibodies from the genital tract of CAP256 were also sensitive to K169E in the CAP45.G3 virus. The presence of N332-dependent antibodies in both genital secretions and plasma from CAP255 was demonstrated using the TRO.11 virus. Although the level of neutralization against the wild-type
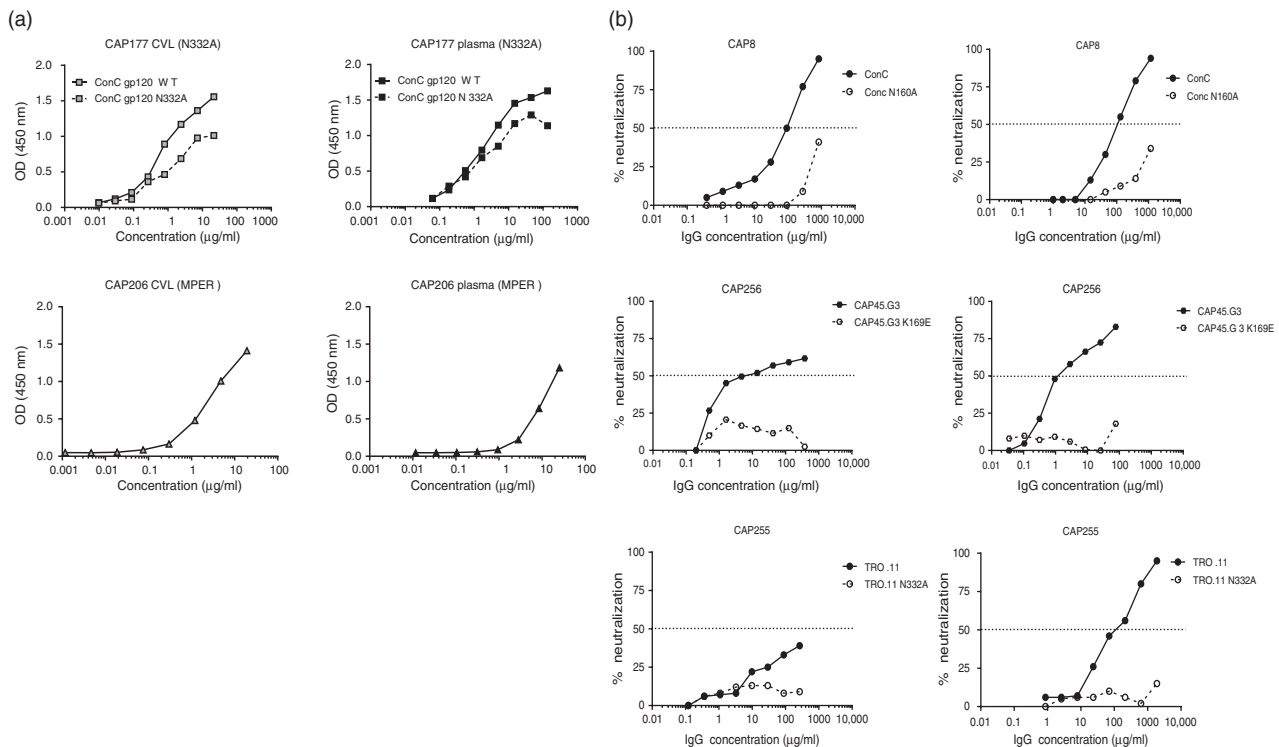
Fig. 5. Epitope mapping of antibody specificities by ELISA (a) and neutralization (b). Cervicovaginal lavage and plasma immunoglobulin (Ig)G antibody specificities in CAP177 at 3 years postinfection were tested by binding to wild-type and N332A mutant gp120, whereas anti-MPER IgG activity in CAP206 was detected at 3 years postinfection in both genital tract and plasma by peptide ELISA (a). Plasma and genital tract IgG antibody from CAP8, CAP256 and CAP255 were mapped by measuring neutralization of wild-type virus and mutant viruses. The dotted lines represent IC_{50} values (b).

virus was less than 50% inhibition (probably because of low levels of recoverable HIV–specific antibody), there was almost complete knockout with the N332A mutant. Overall, these data reliably confirmed the presence of identical HIV–specific antibody specificities in both genital secretions and plasma.

Discussion

We have detected HIV–specific binding and neutralizing IgG antibodies in the female genital tract of HIV-infected women previously shown to have bNAbs in plasma. Overall, these IgG antibodies matched those in plasma, targeting major neutralizing antibody epitopes including V2 and V3 glycans and the MPER of gp41. Binding antibodies to the V1V2 region, previously shown to correlate with protection in the RV144 HIV vaccine trial [12], were also present in the genital tract. The similarity of the antibody specificities detected in genital secretions and plasma suggest that the HIV–specific antibodies (or B cells) are able to transude across the genital mucosa. This further suggests that antibodies elicited by systemic vaccination (or transferred through passive immuniz-ation) are likely to reach mucosal surfaces and could contribute to preventing the sexual transmission of HIV.

This study has confirmed earlier reports that HIV–specific responses in genital secretions are almost exclusively of the IgG isotype [13,14,21,54]. The paucity of HIV–specific IgA despite abundant levels of total IgA in lavages of HIV-infected women has also been noted by others [19,55–57]. A similar lack of HIV–specific IgA is seen in other mucosal external secretions including breast milk although in digestive mucosal secretions, such as saliva and intestinal surfaces, HIV–specific IgA antibodies predominate [58–60]. Even though IgG is the dominant isotype in the genital tract, the levels of total IgG have been reported to vary during the phases of the menstrual cycle [61,62]. In this study, sampling of genital secretions was not normalised according to cycle as our focus was on examining the functional properties of genital antibodies which are unlikely to be affected by the menstrual cycle. Interestingly, HIV–specific IgG could be recovered from patients on long-term ART indicating that removal of antigenic stimulation did not ablate the IgG response in the genital compartment.

Mucosal sampling is particularly challenging for measuring antibody neutralization because of the low levels of IgG in genital secretions as well as interfering components [63]. We therefore isolated and quantified IgG prior to performing neutralization assays. This resulted in variable HIV–specific IgG content (the ratio

of HIV specific IgG to total IgG) probably because large and variable volumes are recovered by CVL. Antibody recovery was significantly improved through the use of the cervical Softcup [64,65], which provided more consistent data and higher IgG recovery from genital fluids. The Softcup collects undiluted samples that are processed immediately [38], and thus are not exposed to freeze−thaw cycles, which may reduce the concentration of IgG antibodies in CVL [66]. Furthermore, other studies have shown that the endocervix, which is more specifically sampled by Softcup, has more concentrated antibodies than the vagina [60], which is a washout mainly of the vaginal vault. Another possible explanation for the improved recovery of genital IgG is that the Softcup method retains mucus during processing, which has been shown to harbour antibodies and other antiviral proteins [67], whereas during CVL processing mucus is spun down and discarded. The Softcup thus provides a significant improvement on CVL sample collection for the analysis of the humoral immunity to HIV.

The HIV-specific IgG binding activity to most Env antigens tested was similar for plasma and CVL, except for V1V2 antigens where lower concentrations of IgG at the genital tract made it difficult to detect epitope-specific responses. Although HIV Env-specific IgG reactivity, which encompasses IgG1−4 isotypes, was observed in all individuals, only two had detectable IgG3 responses. These normally short-lived antibodies [68,69] were detected up to 3 years postinfection in plasma and CVL. V1V2-specific IgG3 antibodies were shown to correlate with decreased risk of HIV infection in the RV144 trial [10−12]. Although we were unable to detect V1V2 IgG3 at the genital tract, we suspect this is simply because of lower concentrations in CVL rather than selective exclusion of these antibodies.

The finding of identical specificities among genital and plasma neutralizing IgG antibodies strongly supports a link between the female genital mucosa and blood. This suggests transudation of antibody from blood across the genital mucosa; or trafficking of B cells from the systemic compartment to become resident mucosal antibody secreting cells [60]. A recent study showed recruitment of IgG-secreting plasma cells to the genital tract of vaccinated rhesus macaques as well as a distinct set of resident cervical reserve epithelial cells that delivered IgG to the lumen via the neonatal Fc receptor [70]. The high expression of FcRn reserve cells in the epithelial layer offers a mechanism by which IgG from the circulation is transferred to the lumen and genital tract external surfaces. Several vaccine studies in humans and primate models have shown HIV or SIV-specific IgG antibodies in the genital tract [71,72], providing further evidence of transudation of antibodies either from the circulation or migration of plasma cells to the mucosa.

Even though it was not possible to test large panels of viruses because of limited volumes, this study suggests that HIV-specific bNAbs are present in the female genital tract, and overlap in specificity with those present systemically. This study of women naturally infected with HIV provides pertinent insight into which plasma-derived protective antibodies can transude to the genital tract. Our data suggest that systemic vaccine induced or passively infused antibodies would migrate to the genital compartment where they could protect against invading HIV particles.

Conflicts of interest
There are no conflicts of interest.

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