suggested the possibility of other intrinsic or extrinsic factors beyond those already known, such as reproductive health practices and female genital microbiomes.[11,12]

Success in the establishment of a prospective cohort of patients with acute HIV infection, with body specimens carefully collected from the same individuals before and after infection, is worth congratulating. Results that will emerge from the prospectively collected body specimens will make the group world leaders in HIV vaccines and HIV cure research. Nevertheless, one of the most important contributing factors for success was the non-monetary, effective, and sustainable socioeconomic intervention targeting the needs of this population to encourage participant adherence. The training and job or school placement offered by these investigators to address poverty and the scarcity of opportunity in the studied population, although not designed to assess the effect on HIV acquisition, is indeed a real-life, human-development effort that other biomedical researchers can follow. Finally, we are certain that the investigators of this cohort will be able to show in the future that such a humane intervention can also prevent HIV acquisition in itself.

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The effect of ART on cervical cancer precursor lesions

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In the *Lancet HIV*, Helen Kelly and colleagues[1] present a meta-analysis of the effect of antiretroviral therapy (ART) on high-risk human papillomavirus (HPV)-induced cervical lesions in women living with HIV.[1] As the authors note, cervical cancer is the most common cancer affecting women in low-income and middle-income countries (LMIC)[2] and the most common cancer in women living with HIV.[3] For this reason, most HIV management guidelines recommend frequent colposcopy for this population,[4] an unpleasant procedure for patients and a resource burden on many health systems.

Cervical cancer is caused by a persistent high-risk HPV infection and develops through a series of well defined precursor lesions, named cervical intraepithelial neoplasia (CIN). CIN lesions are graded 1–3 according to the degree of epithelial atypia. Low-grade CIN (CIN1/2) mainly result from a productive HPV infection and are likely to regress after virus clearance. High-grade CIN lesions (CIN2+) harbour a so-called transforming HPV infection and can develop within 3 years after a persistent high-risk HPV infection. Progression to cervical cancer might take another 10–30 years.[5] Infection with HIV is an important risk factor for a persistent high-risk HPV infection and the development of CIN2+ and cervical cancer.[6] The high prevalence of high-risk HPV in women living with HIV and the assumed increased cancer risk indicate that a better understanding of the associations

between viral infections, treatment, and cervical pathogenesis is needed to allow for effective cancer prevention strategies in this population.

In their meta-analysis, Kelly and colleagues aimed to review and summarise the evidence on the association of ART with high-risk HPV prevalence, and with CIN2+ prevalence, incidence, progression, and regression. Secondly the role of HIV-related cofactors that might modify these associations, such as duration and timing of ART, initiation of ART, immune suppression, and recovery were investigated. The researchers unveiled some findings one might expect on the basis of the ART attributed immune restoration effect. Women living with HIV on ART have a lower prevalence of both high-risk HPV and CIN2+ lesions. Furthermore and as expected, a reduction in the incidence and progression of CIN2+ lesions were seen in women on ART, and an increase in regression of CIN2+ lesions. Notably, these effects remained after adjusting for immune restoration indicators such as CD4 cell count and duration of ART use.

Strong points of this study are the subanalysis on the level of timeperiod and geographical location of the included studies. Some striking discrepancies caused by study heterogeneity were brought to light. On the one hand, studies from Africa, Europe, and North America overall found a preventive effect of ART on cervical lesion incidence and progression and promotion of regression. On the other hand, studies from Latin America and Asia reported an overall increased risk of high-risk HPV and CIN2+ lesions among women on ART compared with treatment-naive women. The latter is counterintuitive if one assumes that ART induced immune restoration would reduce high-risk HPV-associated morbidity. The authors propose the explanation that the Latin American and Asian studies involved a generation of women who might have started ART under older guidelines at lower CD4 cell count thresholds and therefore might not have fully recovered their HPV-specific mucosal immune response. Kelly and colleagues mention that there were fewer studies available from Asia and Latin America and most were cross-sectional in design. Still, these heterogeneous findings again indicate that ART initiation irrespective of CD4 cell count in combination with sustained adherence are important for immune recovery and reduce high-risk HPV-associated morbidity.

Kelly and colleagues[1] also offer some practical lessons. Apart from the importance of commencing ART as soon as possible, women with low or unknown nadir CD4 counts should be screened more frequently. Future studies will have to elucidate which women can be screened less frequently on the basis of markers indicating successful immune restoration. Triaging women for colposcopy would relieve overburdened health systems and might reduce unnecessary procedures.

Particularly in LMIC with high prevalence of high-risk HPV and HIV, implementation of effective cytology-based or HPV-based screening programmes has proven difficult. Research shows[7,8] that molecular methylation tests aimed at the detection of lesions resulting from a transforming high-risk HPV infection (high-grade CIN and cancer), might provide an interesting selection method for women living with HIV in LMIC. Further development of rapid point-of-care tests would allow women to be (self) screened and depending on local facilities potentially treated in one day, thereby preventing loss to follow-up.

Furthermore, future research in the line of Kelly and colleagues' could be applied to anal cancer screening in HIV-positive men who have sex with men. Triaging men for high resolution anoscopy to screen for anal precursor lesions would be welcomed for the same reasons.[9]

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HJCdV has received grants from MSD. RDMS holds minority shares in Self-screen BV and has a patent for Methylation markers for cervical cancer detection.

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Point-of-care viral load testing and differentiated HIV care

WHO recently approved the first quantitative point-of-care (POC) HIV viral load assay for use in resource-limited settings.[1] The Xpert HIV-1 VL (Cepheid, Sunnyvale, US) requires 1 mL of plasma to measure viral load in 90 min on the GeneXpert platform. The assay has been validated in several clinical settings[2,3] and detects virological failure (>1000 copies per mL) with 94% sensitivity and 99% specificity.[1] Current costs seem similar to existing laboratory technologies, with four module GeneXpert platforms available at US$17 000 and cartridges at $17 (excluding tax and shipping).[2] Prequalification will allow the Xpert HIV-1 VL to be procured through WHO tender processes, facilitating expanded access at lower costs, particularly in low-income and middle-income countries. This could be an important milestone for HIV programmes, as POC viral load testing has potential to fill gaps in coverage and to change the way HIV care is provided, through more efficient client-centred services.

As access to antiretroviral therapy (ART) increases, global demand for viral load monitoring is estimated to grow from 7 million tests in 2013 to 15–30 million in 2018.[4] Scale-up is particularly challenging in southern Africa because of a paucity of trained laboratory personnel, high costs of centralised laboratory infrastructure, and challenges with specimen transport and return of results.[5] POC viral load assays such as the Xpert HIV-1 VL may allow decentralised viral load testing that circumvents some of these problems. Automated systems allow operation by non-laboratory personnel, while near patient testing can eliminate the need for specimen transport. However, POC testing capacity will need to match numbers of patients with clinic flows adapted to minimise turn-around times. Technological advances to speed up sample processing will be important, as will fingerprick and dried blood spot testing, which are currently not available on Xpert HIV-1 VL. Several other quantitative POC viral load assays have been validated in decentralised clinics in southern Africa, including the SAMBA I/II semi-Q (Diagnostics for the Real World Ltd., Cambridge, UK),[6] Alere Q NAT (Alere, Waltham, MA, US),[7] and Liat HIV Quant (Roche Diagnostics, Basel, Switzerland).[8] While the widespread availability of the GeneXpert platform for tuberculosis diagnostics might favour the introduction of the Xpert HIV-1 VL, most machines are situated within centralised laboratories, reflecting the remaining challenges of implementing POC molecular diagnostics within existing care models.

The advent of POC viral load technologies coincides with the development and roll-out of new models of efficient, client-centred HIV care in low-income and middle-income countries.[9] These differentiated care services aim to increase health system capacity and quality and have typically focused on providing ART to stable clients through community adherence groups, decentralised ART pick-up points, task shifting between health-care professionals and lay workers, and reducing the frequency

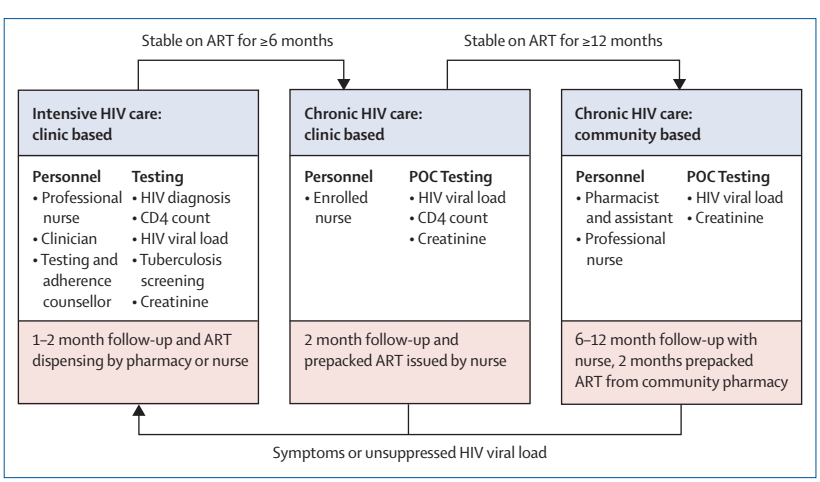

Figure 1: **Conceptual model of differentiated HIV care and integrated point-of-care viral load testing, adapted from STREAM[10]**