of transmission outweighs the risk of adverse effects.[7] This finding means that dolutegravir-based regimens can be extended to all women of reproductive age, regardless of pregnancy intent or risk of unintended pregnancy, and women with suboptimal viral suppression on other regimens can be switched to dolutegravir during pregnancy to achieve and maintain viral suppression. However, because safety concerns around dolutegravir taken from conception remain,[8] women receiving dolutegravir-based regimens need to be closely monitored throughout pregnancy and breastfeeding for adverse events, including pregnancy, birth, neonatal, and infant outcomes.[9]

The occurrence of the three transmission events serves as a reminder that dolutegravir in pregnancy alone will not eliminate mother-to-child transmission. Preventing HIV acquisition before and throughout pregnancy and breastfeeding is necessary. Although partner tracing, testing, treatment for people who are HIV positive, medical circumcision in men who are HIV negative, and condom distribution and use are essential, pre-exposure prophylaxis for women at risk of HIV acquisition in pregnancy should be considered.[10] Lastly, preventing unintended pregnancies among women at risk of acquiring HIV and among women living with HIV should remain a priority of programmes for the elimination of mother-to-child transmission of HIV in sub-Saharan Africa.[2]

I declare no competing interests.

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A cure for HIV: how would we know?

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See Articles page e340

With the need for lifelong treatment of HIV with antiretroviral therapy (ART), and the associated costs, adverse events, and stigma, there is a growing need and a global scientific effort to find a cure, with many interventions being currently assessed in animal models and clinical trials.[1] But what does a cure for HIV mean and how can scientists really know that someone is indeed cured?

In *The Lancet HIV*, Ravindra Kumar Gupta and colleagues describe follow-up with extensive tissue and blood sampling[2] of an individual (referred to as the London patient) whose case was originally reported 12 months ago.[3] The London patient is a man living with HIV who was diagnosed with Hodgkin disease and who received a stem-cell transplant from a donor who carried a mutation in the *CCR5* gene (*CCR5*Δ32/Δ32). CCR5 is a key receptor for most strains of HIV and, therefore, T cells or macrophages that do not express CCR5 are protected from infection with strains of HIV that use this receptor.

After transplantation and cessation of ART, Gupta and colleagues report that the London patient's plasma HIV RNA has remained undetectable for 30 months.[2] This period is indeed a very long time to remain aviraemic off ART, considering the median time to viral rebound after cessation of ART is 2–3 weeks. The investigators also assessed semen and cerebrospinal fluid, and samples of gut, lymph node, and rectal tissue. Low levels of HIV DNA were found in lymph node tissue and in blood $CD4^+$ T cells, whereas all other samples were negative for HIV DNA. Importantly, the low levels of HIV DNA that were found were not intact, consistent with archived viral fragments that cannot replicate. Finally, Gupta and colleagues developed

a mathematical model to predict the chance of viral rebound after stopping ART, based on the number of infected cells (the size of the reservoir) and the number of susceptible target cells, estimated by the degree of chimerism or the proportion of donor cells relative to recipient cells.[2] Based on the London patient having greater than 90% chimerism in circulating T cells, they concluded that the chance of future viral rebound while off ART is negligible. With more prolonged follow-up and now tissue sampling, is the London patient really cured?

One difficulty in quantifying persistent virus in an individual on ART is that the ability to detect an infected cell is dependent on the total number of cells tested, which has an upper limit, particularly when sampling tissue sites. A second individual (Timothy Brown, sometimes referred to as the Berlin patient) received a stem-cell transplant from a *CCR5*Δ32/Δ32 donor and has been off ART for more than 13 years with undetectable plasma HIV RNA. This patient also had extensive blood and tissue sampling to find infected cells,[4] and no virus was detected in almost all samples except for some blood samples and one sample from rectal tissue, in which traces of HIV were detected. At the time of testing, this finding was thought to represent low-level contamination of the assay.[5] We now know that most virus that persists on ART is defective and unable to replicate, and we are able to better quantify intact and defective virus with either near full-length sequencing[6] or PCR-based assays.[7] Therefore, a cure for HIV might be better defined as no intact virus, rather than no detectable virus.

What about the immune response to the virus? Could this be a helpful strategy to define a cure? Previous work has suggested that less HIV antigen means less stimulation of antibody production. Therefore, a lower frequency of infected cells on ART has been associated with lower concentration and avidity of anti-HIV antibodies and fewer specific bands on an HIV-specific western blot assay.[8] In both the London patient and Timothy Brown, detection of antibodies to HIV proteins diminished after transplantation and gradually declined over time, but these antibodies still persisted.[3,5]

A key question now for the area of HIV cure is how soon can one know if someone has been cured of HIV? Prolonged clinical observation and follow-up is required, with regular testing of plasma HIV RNA. But if, over time, the chance of viral rebound becomes less likely, could the frequency of testing be reduced and one day even stopped? Reduced frequency of monitoring for disease relapse over time is a common practise in follow-up of many malignant diseases. However, the duration and frequency of follow-up in such as setting is based on very large cohorts with a deep understanding of the natural history of the specific malignant disease. We will need more than a handful of patients cured of HIV to really understand the duration of follow-up needed and the likelihood of an unexpected late rebound in virus replication.

The finding of no intact virus in both blood and tissue can be reassuring for a patient who might face great anxiety and uncertainty about whether and when viral rebound off ART might occur, which in other settings has been completely unpredictable.[9,10] In view of the many cells sampled in this case, and the absence of any intact virus, is the London patient truly cured? The additional data provided in this follow-up case report is certainly exciting and encouraging but, in the end, only time will tell.

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How universal does universal test and treat have to be?

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See Articles page e348

HIV treatment as prevention, not only of HIV-related disease but also of transmission, was proposed in 2006 as a means to end the epidemic.[1] Several influential studies and models predicted that early treatment of most people who live with HIV (PLWH) could reduce HIV transmission rates to near zero, at the population level.[1–3] As a result, treatment as prevention evolved into the universal HIV test-and-treat (UTT) approach, which entails offering HIV counselling and testing to an entire population and ART to all PLWH. In 2014, UNAIDS announced ambitious new goals to "end AIDS by 2030" by reaching 90-90-90 targets by 2020: 90% of PLWH knowing their status, 90% ART coverage among those knowing their status, and 90% viral suppression among people on ART.

Great progress has been made, with an estimated 79% of people having been diagnosed, 62% of individuals aware of their status being on ART, and 53% of those on ART being virally suppressed globally, although heterogeneity exists between countries.[4] However, until UTT community-based trial results began to be reported 4 years ago, it remained unclear to what extent this remarkable increase in coverage translated into HIV prevention. In *The Lancet HIV*, Adam Akullian and colleagues[5] report that ART scale-up in eSwatini, which has the world's highest HIV prevalence, has largely been a success story, dramatically reducing adult HIV incidence and mortality. Using a mathematical model calibrated with demographic, HIV prevalence, and ART coverage data, they estimate that adult mortality decreased by more than 50% and HIV incidence by more than 40%, between 2010 and 2016. However, Akullian and colleagues also predict that with ART coverage maintained at current levels, HIV incidence will remain above 1 per 100 person-years—far above the target of 1 per 1000 person-years defined as representing epidemic control. Importantly, even 100% ART coverage within an average of 6 months since infection acquisition (implying annual universal HIV testing with 100% coverage), would reduce adult HIV incidence to 0·73 (95% CI 0·55–0·92) per 100 person-years by 2030 and 0·46 (0·33–0·59) per 100 person-years by 2050—still far off the epidemic control target.

These findings concur with results of the UTT trials. Substantial reductions in HIV incidence were observed in study communities because ART access improved in both intervention and control groups (where standard of care was offered), but no significant differences in population-level HIV incidence reductions were found by study group, with HIV incidence reductions due to ART falling far short of epidemic control.[6] It seems logical that 90-90-90 levels would be insufficient to end the epidemic, as such coverage implies that 27% of PLWH would remain virally unsuppressed and capable of HIV transmission. But why have Akullian and colleagues predicted that UTT at even higher levels of ART coverage, at 95-95-95 and beyond, will not end the HIV epidemic, when previous models came to much more positive conclusions in similar settings (figure)?

Reasons the authors posit are HIV transmissions during the elevated infectiousness of early HIV infection and demographic gaps in testing, treatment, and viral suppression coverage. Treatment coverage is lower in younger age groups in eSwatini, particularly among young men. If these and other demographic groups that UTT misses are disproportionate transmitters of HIV infection, the population-level effectiveness is compromised. Early models of UTT were criticised for not adequately addressing behavioural heterogeneity or the natural history of HIV infection.[2] Since then, the modelling community has attempted to explore reasons for differences in model predictions between research groups. More real-world data from treatment-as-prevention studies have reduced variability in predictions, but differences remain. Hontelez and colleagues[7] developed nine structurally different models of the South African