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MAJOR ARTICLE

Review of the current TB human infection studies for use in accelerating TB vaccine development: A meeting report

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Tools to evaluate and accelerate tuberculosis (TB) vaccine development are needed to advance global TB control strategies. Validated human infection studies for TB have the potential to facilitate breakthroughs in understanding disease pathogenesis, identify correlates of protection, develop diagnostic tools, and accelerate and de-risk vaccine and drug development. However, key challenges remain for realizing the clinical utility of these models, which require further discussion and alignment amongst key stakeholders. In March 2023, the Wellcome Trust and the International AIDS Vaccine Initiative (IAVI) convened international experts involved in developing both TB and Bacillus Calmette-Guerin (BCG) human infection studies (including mucosal and intradermal challenge routes) to discuss the status of each of the models and the key enablers to move the field

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forward. This report provides a summary of the presentations and discussion from the meeting. Discussions identified key issues, including demonstrating model validity, to provide confidence for vaccine developers, which may be addressed through demonstration of known vaccine effects, e.g. BCG vaccination in specific populations, and by comparing results from field efficacy and human infection studies. The workshop underscored the importance of establishing safe and acceptable studies in high-burden settings, and the need to validate more than one model to allow for different scientific questions to be addressed as well as to provide confidence to vaccine developers and regulators around use of human infection study data in vaccine development and licensure pathways.

Keywords: Human infection studies; human challenge studies; controlled human infection; Tuberculosis; vaccines

INTRODUCTION AND BACKGROUND

Each year, tuberculosis (TB) kills more people globally than any other single infection, surpassing the number of deaths caused by COVID, resulting in approximately 1.6 million deaths in 2021[1]. An estimated 10.6 million people progressed to active TB disease in 2021, with approximately 1% of the world's population newly infected with *Mycobacterium tuberculosis* (*M.tb*), the bacterium that causes TB[1]. Treatment regimens are complex and lengthy, with consequent treatment adherence challenges. Drug-resistant strains are a growing problem in many countries, affecting around 500,000 people each year[1] thus new TB vaccines are essential for global TB control strategies.

Effective vaccination is a critical tool to promote long-term TB control. The only licensed TB vaccine, BCG, is derived from *Mycobacterium bovis (M.bovis)*, the cause of bovine TB, and was developed more than a century ago. BCG is effective in preventing severe, disseminated forms of TB in infants, but offers only variable and incomplete protection against TB in adolescents and adults [2,3]. The TB vaccine development pipeline is skewed, with few candidate TB vaccines in early-stage development. While progress has been made with several candidates in late stage clinical development[4], vaccine development for TB has proven extremely challenging due to an incomplete understanding of protective immunity and the lack of well-defined correlates of immune protection against the development of active TB, as well as uncertainty as to the predictive value of animal models[5–7]. In 2023, the WHO established the TB Vaccine Accelerator Council committed to facilitate the use of novel TB vaccines by aligning funders, governments, and global agencies to identify and overcome barriers in TB vaccine development[8,9].

TB human infection studies are being developed to accelerate new TB vaccine development, by enabling identification of vaccines capable of preventing or eliminating carefully controlled mycobacterial challenges administered to vaccinated volunteers. Human infection studies have been established for both **respiratory/mucosal challenge** (administration to the lung) and

intradermal challenge (skin administration) [10,11]. Each has its own advantages and disadvantages (**Table 1**). Studies to date have shown that models based on both lung and skin routes of BCG challenge agent administration are **safe and well-tolerated**, and extensive information has been collected on **immune responses following challenge.** These studies are designed to provide early proof of concept of the activity of TB vaccine candidates against mycobacterial challenge, to support down-selection of candidates and prioritisation for later-stage field trials, identify correlates of protection, and develop diagnostic tools.

In March 2023, Wellcome and IAVI convened an international workshop to discuss the status of TB human infection studies globally and prospects for the future. Sessions focused on lung and skin challenge models, conditionally replicating *M.tb* strains as alternatives to BCG challenge, and the potential for studies in high-burden countries.

DISCUSSION

Ethical considerations & limitations

Discussions on the ethics of human infection studies have included the safety and conduct of these studies. In 2022, WHO published an ethics framework for the conduct of human infection studies including criteria for consideration such as challenge strain selection; justifications for conducting these studies; potential risks to the volunteers and third parties; and the responsibilities of researchers and others involved in ensuring risks are minimal[12]. The guidance also includes a case study on an aerosol BCG study recruiting volunteers who had been treated for TB or exposed to TB within their household[13]. The study highlighted the potential limitations of using BCG as a surrogate challenge agent for *M.tb*, however currently a challenge study with virulent *M.tb* would not be acceptable due to the risks to volunteers. A TB disease model would also be difficult ethically at present due to the potential risk of lengthy multi-drug treatment regimens with the risk of drug-resistant TB strains emerging if therapy is incomplete, and potential disease complications to the volunteer. Safety of the volunteer in these studies is paramount and whilst most human infection studies are conducted using a wild-type virulent strain these studies have a good safety record due to multiple risk mitigations being in place such as a known highly effective and short treatment and availability of reliable diagnostics[14].

Human infection studies have demonstrated utility for monitoring a vaccine/intervention impact on prevention of infection, however their suitability for assessing efficacy of products that function by preventing progression from infection to disease may be limited. For example, a negative result in a human challenge model for TB infection does not necessarily mean that the vaccine candidate would not prevent disease. For TB, challenge models that can estimate total mycobacterial replication by Area-Under-the-Curve (AUC) analyses over 2 months post-challenge *in vivo* may provide more relevance for detection of immunity protective against disease progression[15]. Further discussion on the ethics of BCG versus *M.tb* human challenge and an infection model versus a disease model was expanded in a subsequent meeting

in late 2023, outputs of which will be disseminated in a report. There was a consensus however that TB human infection studies should be used to provide signals of efficacy and not attempt to model clinical disease due to safety concerns.

Challenge agents

Bcg

Most studies have delivered **BCG** as the challenge agent, as Good Manufacturing Practice (GMP)-quality product is available and bacterial growth is contained in immunocompetent recipients such that it is considered safer than using *M.tb*[16]. The assumption is that cell-mediated immune responses are likely to be similar following BCG and *M.tb* challenge. Concerns have been expressed, however, as to whether BCG challenge models represent reliable predictors of the ability of candidate TB vaccines to prevent *M.tb* infection. However studies have shown that BCG vaccination can demonstrate a protective effect in both the skin and aerosol BCG challenge model[10,17].

BCG was developed in the 1920s by serial propagation of *M.bovis* to attenuate its virulence. Loss of virulence is now known to be caused by deletion of the **RD-1 locus**, which includes nine genes, including potential vaccine targets. *M.bovis* and *M.tb* are genetically very closely related (>99% identical) and *M.bovis* retains the ability to infect humans[18]. A caveat of delivering BCG in a challenge model is that BCG does not contain RD1 antigens so would not be appropriate for assessing RD1 antigen-containing vaccines.

Conditionally replicating *M.tb*

An ideal *M.tb* challenge would retain as many of the wild-type features of *M.tb* as possible, show periods of growth in volunteers, and be survival-dependent on an exogenous compound so that bacteria die when the exogenous compound is withdrawn. The CHIM-TB project, a US-led research collaboration is developing conditionally replicating *M.tb* strains that could provide a more *M.tb*-like challenge[19].

Conditionally replicating *M.tb* strains have been developed that incorporate a mechanism that ensures microbial growth is only possible in the presence of two inducers, tetracycline and trimethoprim. A tetracycline-controlled module represses the synthesis of phage lysin when tetracycline is present. The second mechanism is protein-based, with an essential protein linked to a domain that is stabilised in the presence of trimethoprim. Having two mechanisms provides additional safety, as it is possible for escape mutants to arise and disable the growth control switch. Individually, escape mutants arise at low frequency (c. 5×10^{-9} per generation for the tetracycline system) and the effects are additive, bringing escape rates down to levels lower than the limit of detection. The strains have been shown to behave as expected in immune-competent mice, immune-deficient mice and non-human primates, confirming preclinical proof of concept[19].

Safety and rate of reversion to wild type will be a key consideration for clinical translation and will be discussed with regulators.

The goal in a TB human infection study is to challenge with a very low biologically relevant challenge dose of *M.tb* and never allow the infecting bacterial population to reach high numbers. The most feasible readouts are immune correlates of establishment of *M.tb* infection and burden. These need further validation but include quantitative measure of the Interferon-γ (IFN-γ) producing T cell response to ESAT-6 and CFP-10 in people who are immunologically naïve to *M.tb* infection[20]. Other possible measures include positron emission tomography–computed tomography (PET-CT) imaging, humoral responses, or more speculatively, bacterial reporter assays currently in development[19].

While proof of concept of conditionally replicating *M.tb* strains has been demonstrated in animal models, the strains need to be reconstructed to meet at minimum the principles of GMP before they can be used in a human challenge study.

Lung challenge models

Lung human infection models have the advantage that they best mimic the **natural aerosol route of infection** and, to date, have used BCG as the challenge agent. BCG can be delivered to the lungs via a **nebuliser** or by **bronchoscopy**. The former best reproduces the natural route of *M.tb* infection. The latter is more invasive but enables lung mucosal dose delivery to be more precisely controlled. In addition, the site of administration can be accurately defined, with samples taken repeatedly from this site, and results can be compared with those from samples taken elsewhere in the lungs of the same individual. In addition, the different lung segments in one individual can be used to assess a vaccine and control at the same time. Studies in South Africa have demonstrated the feasibility of this approach i.e., undertaking the bronchoscopic administration of both live BCG and the control at the same time, with safety comparable to that seen with conventional bronchoscopy[13]. Another route which has been less explored is nasal administration, which could be comparable to the lung human infection model in mimicking disease. Evidence for nasal administration exists with SARS CoV-2[21] and pneumococcal human infection studies[22].

Using the nebulisation route, a less invasive approach than bronchoscopy, doses loaded into the nebuliser (approximately 10^7 CFU) are around two to three times higher than with bronchoscopic administration because of 1-2 log CFU losses using this mode of delivery[23]. Whilst it is not possible to directly measure how many bacteria get to the alveolus, exposure in the lung is likely to be similar between both approaches. Unlike bronchoscopic administration, the site of infection cannot be restricted to a specific area of the lungs when using a nebuliser, but this route best reproduces the natural route of infection.

Sampling for analysis of microbial growth and immune responses is generally by **bronchoalveolar lavage (BAL)**. BAL samples can be used for culture, PCR or other detection methods, as well as for immunological and transcriptomic analyses[11]. Analysis of blood samples can provide

complementary data on systemic immune responses at the same time points. The limited quantity of material in BAL samples, however, can make it difficult to carry out both microbiological and immunological analyses. In addition, variation in the volume of samples obtained makes quantification more difficult than with punch biopsies of skin. Therefore, the lung challenge model may be less sensitive and require larger samples sizes compared to the skin challenge model.

Initial studies have focused on safety and identifying the optimal challenge dose through dose-escalation studies in BCG-naive volunteers. Experience to date suggests that both nebuliser and bronchoscopic administration is **safe and tolerable**, and recovery of BCG from BAL fluid samples is possible[24,25].

Immunogenicity analyses following lung challenge with BCG, using blood and BAL samples, have provided insights into cytokine and T-cell subset responses, revealing a Th1-type response and strong CD8+ T-cell responses[10]. Stronger responses are seen in lung samples compared to blood samples. Ongoing studies are analysing BAL samples at multiple time points to provide data on the dynamics of immune responses. A UK study is also planned to analyse responses in volunteers previously immunised with BCG[24].

Bronchoscopy-based studies have been carried out in South Africa, with the aim of assessing immune responses following challenge. These studies have considered host variability, by stratifying volunteers according to likely susceptibility to infection[5]. Participants were selected from households with a confirmed case of active TB, increasing the likelihood of exposure to *M.tb*. Clinically, participants have fallen on a spectrum from those remaining uninfected with *M.tb* despite the likelihood of ongoing exposure, to persons manifesting repeated episodes of TB disease. Comparison of changes in gene expression has identified a possible signature associated with risk of infection, which could be used to stratify or select volunteers for human infection studies or trials[26,27].

Developing sufficiently sensitive systems capable of detecting and quantifying bacterial load, especially in the lung models, may be the most difficult aspect of the use of these strains in human infection studies. Enzymatic amplification methods are being explored, as the number of challenge microbes used is likely to be small, making direct detection of bacteria difficult. In TB uninfected participants, interferon gamma release assay conversion may serve as a meaningful endpoint. PCR-based methods are sensitive and specific but do not necessarily provide an indication of living challenge strain cell numbers. An *ex vivo* **mycobacterial stasis assay** assessing *M.tb* antigen-stimulated effector T-cell function, has been used to demonstrate the impact of several immune mechanisms on *M.tb* survival[28,29]. This method has also been applied to assess alveolar and blood samples from clinical studies, including human infection studies[28,30,31].

A further gap in knowledge relates to the **trafficking of *M.tb*** in lung challenge models. Alveolar space is typically cleared rapidly, so disappearance of *M.tb* could reflect translocation through cells and trafficking to cervical, axillary, or mediastinal lymph nodes[32]. This is also observed

with the skin challenge model with clearance of *M.bovis* antigens to the axillary lymph nodes[33]. PET-CT imaging may be a possible method for tracking translocation.

In terms of vaccine assessment, a key consideration is whether **a known vaccine effect** can be demonstrated in the lung challenge model to provide confidence that it is a reliable mimic of natural infection and can be used to demonstrate a protective effect of vaccination against *M.tb* infection. As with all models, **'back-validation',** i.e., comparing the results of field efficacy studies with those from human infection studies, would provide confidence in the reliability and predictive power of a model for the prevention of TB infection.

TB vaccine development potentially could be accelerated if **regulatory authorities** were willing to accept data from human infection studies for licensure. The extent to which regulatory authorities may accept TB human infection study data for this purpose remains a question. Currently it seems unlikely that a regulator would accept a TB human infection study as sufficient for licensure. The real value of these studies would be to de-risk and prioritise vaccine candidates in early clinical development.

Skin challenge models

Intradermal administration of challenge strains has the advantage of being **less invasive** than lung challenge models, which require bronchoscopy for administration and/or sample collection. **Skin punch biopsy** is a highly standardised routinely conducted procedure and provides a consistent volume of material for analysis. Microbial load can be readily assessed through culturing or molecular methods (PCR). As skin administration is the licensed route for BCG vaccination, regulatory approvals for human infection studies are typically more straightforward. However, the relationship between immune responses generated by candidate TB vaccines assessed in the skin (or blood), and protective responses in the lung is unclear. The main drawback concerns the relevance of clearance kinetics of intradermal mycobacterial challenge to predicting the impact of TB vaccines on preventing *M.tb* infection or the development of TB disease.

Multiple skin human infection studies have been carried out in the UK, USA, and other countries, including low- and middle-income countries (LMICs)[10]. These studies have demonstrated that such skin challenge models are **safe and tolerable** and can be used to track immune responses following challenge, although significant reactogenicity has been seen at high doses[15,16].

A protective effect of past BCG vaccination against skin BCG infection, mirroring the known effect of BCG vaccination against virulent *M.tb* infection, has been demonstrated in a range of small and large animal models [34–36]. Furthermore a protective effect of prior BCG vaccination on a subsequent BCG skin challenge has been demonstrated in humans, mirroring the known protective effect of BCG in the UK population[10,37]. These data support the biological validity of the skin challenge model. Effects of past BCG vaccination on microbial load may be optimally detected 2 weeks post challenge; earlier may be too soon for a memory response to develop and later may be less sensitive due to bacterial clearance[38].

Rather than mapping bacterial load at specific time points, an alternative approach may be to quantify total microbial numbers during the challenge using an area-under-the-curve calculation, allowing for microbial quantification over a particular time period. A range of methods could be used for quantification, including culture-based methods and PCR. However, inter-individual variation using these methods is high[39]. A method based on analysis of pre-ribosomal RNA synthesis—a **molecular viability test—**may represent an opportunity to reliably quantify living mycobacteria and reduce variability, meaning fewer volunteers would be needed to generate the statistical power to detect vaccine effects[40,41].

A complementary approach may be the use of **fluorescently labelled microbial challenge strains to quantify bacterial load** non-invasively by imaging or by punch biopsy. Studies with the skin challenge model have shown that fluorescently labelled bacterial load can be quantified non-invasively by imaging through the skin, and differences in cell numbers can be identified when responses in previously vaccinated and unvaccinated animals are compared[42]. In BCG-vaccinated mice given an intranasal challenge with *M.tb* and an intradermal challenge with fluorescent-BCG, the decrease in fluorescence in the skin correlates with the decrease in *M.tb* recovered from the lung, suggesting that vaccine-induced changes detected in skin are a good indicator of effects in the lung[42]. Correlations of bacterial load with immune responses will need to be assessed, alongside suitability for use in human volunteers and the sensitivity of the method to detect vaccine effects.

These studies suggest that a skin challenge model is highly **practical and relatively easy to apply**. It is best suited to assessment of systemic immune responses; the relevance of these responses to protective mucosal responses will need to be assessed.

Studies in endemic settings

A recent review revealed that few human infection studies have been carried out in high-burden settings[43]. This may be significant for the TB field as responses to BCG vary by setting and protective immune responses may differ based on past exposure[44]. Discussants emphasised that human infection studies in endemic settings must be carried out with the full support of local communities, address important local questions, and include innovative immunological analysis.

BCG lung human infection studies have been conducted in South Africa, and the case for conducting these studies in other endemic settings is highlighted by the findings of a **pneumococcal human infection model** established in Malawi following technology transfer from the Liverpool School of Tropical Medicine[13,16]. Studies in Malawi were established to understand why the pneumococcal vaccine PCV13 is less effective in Malawi than in the UK. Following extensive community engagement to ensure that the local community was supportive, the pneumococcal human infection model was introduced in Malawi[45]. This study demonstrated that the pneumococcal carriage at volunteer recruitment has a significant impact on vaccine response; when those carrying pneumococcus at recruitment were excluded from analyses, vaccine

efficacy in Malawi was the same as in Liverpool[22]. As pneumococcal carriage is relatively high in Malawi, this could explain the lower effectiveness seen in Malawi and the failure to achieve population immunity.

The BCG skin challenge model used in Oxford is being introduced into Liverpool, where researchers plan to replicate the Oxford study and explore longitudinal and intercompartmental immune responses following challenge. Once established in Liverpool, the potential to follow the pneumococcal human infection model developmental strategy and transfer the model to Malawi will be explored[16].

CONCLUSIONS

Discussions at the meeting highlighted the potential of TB human infection studies and significant progress in the field, and acknowledged that models currently don't have utility in new vaccine development. Key issues to address include **model validity**, through demonstration of known vaccine effects and by comparing results from field efficacy and human infection studies[46]. It is unlikely currently that developers of late-stage vaccines will be willing to allow their vaccines to be tested in human infection studies, but a **demonstration of predictive power** could persuade developers of new candidates to use human infection studies to gain an early indication of vaccine efficacy or to prioritise among candidates.

There was consensus in continuing the development of both the BCG and TB human infection studies for incentivising the TB vaccine field to develop new and better vaccines for TB, and the need to engage with regulators to determine how the data obtained could be used in vaccine licensure determinations. Until new safe strains of *M.tb* are available for testing in a human infection study, much progress can be made using BCG to refine the clinical model approach to route, dose, and endpoints. Participants also highlighted the advantages of human infection studies in **high-burden settings**, since immune responses and vaccine effectiveness may vary according to past exposure history, genetics, and infection status. Critical to ensuring the BCG and TB human infection studies being established progress with an aligned and collaborative approach was the suggestion of a roadmap to allow agreement on the key barriers, gaps in knowledge and the steps needed to accelerate development of validated studies.

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Table 1. Summary of the advantages and challenges of potential BCG/TB human infection studies discussed in the workshop

	Lung challenge models (nebuliser & bronchoscopy-based methods)	Skin challenge models (intradermal)
Platform advantages	• Aerosol route best mimics the natural aerosol route of infection and is less invasive than bronchoscopic administration. • Bronchoscopic administration is more invasive than delivery via nebuliser, but challenge dose and site of administration can be precisely controlled.	• Intradermal administration of BCG is the licensed route for BCG vaccination streamlining regulatory approval for potential clinical studies. • Skin punch biopsies are less invasive and provide a highly standardised procedure for sample collection and quantification of bacterial load by standard analytical methods e.g., PCR. • Safety and feasibility of the model has been demonstrated (with BCG and the vaccine candidate MVA85A)[10,47] • Well suited for assessment of systemic immune responses
Platform challenges	• Intrapulmonary administration of challenge bacteria, such as BCG, is potentially more risky than intradermal challenge. • Obtaining samples by bronchoalveolar lavage is relatively invasive. • Limited sample volume from bronchoalveolar lavage makes quantification of bacterial load difficult.	• Intradermal challenge is not representative of the natural route of infection. • Concerns around the relevance of clearance kinetics of intradermal mycobacterial challenge to predicting the impact of TB vaccines on preventing *M.tb* infection or the development of TB disease.
Potential platform-specific enablers to move the field forward	• Reliable and standardised method to stratify participants according to their susceptibility to develop *M.tb* infection. • Greater understanding of trafficking of *M.tb* from alveolar space. • Demonstration of a known vaccine effect.	• Translation of fluorescently labelled microbial challenge strains to clinical use. • Enhanced understanding of links between systemic and mucosal immune responses, and correlations with protection. • Quantification methods with increased sensitivity to detect a vaccine effect.
Cross-cutting enablers	• Sensitive, reliable, and standardised methods for quantification of bacterial load. • Dialogue with regulatory authorities to assess how data from human infection studies may be considered by regulators as part of the body of evidence when making licensure determinations.	

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Dovato
dolutegravir/lamivudine

EVIDENCE SUPPORTS THE HIGH BARRIER TO RESISTANCE OF DOVATO UP TO 5 YEARS[1-3]

CONFIDENCE IN DOVATO ACROSS TREATMENT SETTINGS[4–9]

Treatment-naïve resistance rates, with up to **3 years of evidence**[5–7]

0% (n=0/1,885)*[,4]
REAL-WORLD EVIDENCE

0.1% (n=1/953)**[,†,‡,§,5–7]
RANDOMISED CONTROLLED TRIALS

Treatment-experienced resistance rates, with up to **5 years of evidence**[1–3]

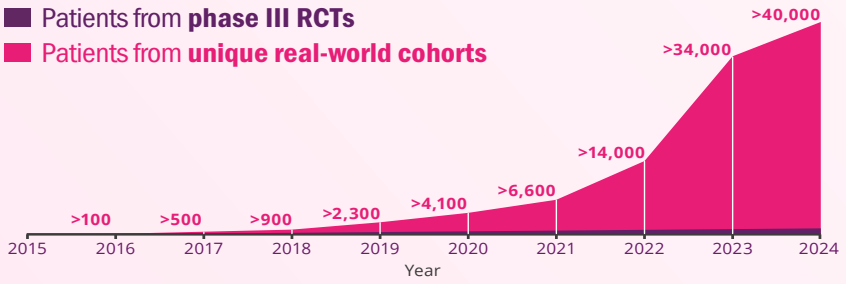
0.03% (n=10/35,888)*[,4]
REAL-WORLD EVIDENCE

0% (n=0/615)[||,¶,#,8,9]
RANDOMISED CONTROLLED TRIALS

>300,000 PEOPLE LIVING WITH HIV HAVE BEEN TREATED WITH DOVATO GLOBALLY[10]

DOVATO is supported by a wealth of evidence, with the outcomes of **>40,000** people living with HIV captured within clinical trials and real-world evidence, including those with:[4–9,11,12]

- **NO PRIOR TREATMENT EXPERIENCE**[13]
- **NO BASELINE RESISTANCE TESTING**[13]
- **HIGH BASELINE VIRAL LOAD** (>100,000 copies/mL and even >1M copies/mL)[6,13]
- **LOW CD4 + COUNT** (≤200 cells/mm³)[13]



IS IT TIME TO RECONSIDER THE VALUE OF THE 2ND NRTI?

LEARN MORE

DOVATO is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults and adolescents above 12 years of age weighing at least 40 kg, with no known or suspected resistance to the integrase inhibitor class, or lamivudine.[13]

Adverse events should be reported. Reporting forms and information can be found at **https://yellowcard.mhra.gov.uk/** or search for MHRA Yellowcard in the Google Play or Apple App store. Adverse events should also be reported to GSK on 0800 221441

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ABBREVIATIONS

3TC, lamivudine; **CD4,** cluster of differentiation 4; **DTG,** dolutegravir; **FDA,** United States Food and Drug Administration; **FTC,** emtricitabine; **HIV,** human immunodeficiency virus; **ITT-E,** intention-to-treat exposed; **NRTI,** nucleoside/nucleotide reverse transcriptase inhibitor; **RCT,** randomised controlled trial; **RNA,** ribonucleic acid; **TAF,** tenofovir alafenamide fumarate; **TDF,** tenofovir disoproxil fumarate; **XTC,** emtricitabine.

FOOTNOTES

*Data extracted from a systematic literature review of DTG+3TC real-world evidence. Overlap between cohorts cannot be fully excluded.

**The reported rate reflects the sum-total of resistance cases calculated from GEMINI I and II (n=1/716, through 144 weeks), STAT (n=0/131, through 52 weeks), and D2ARLING (n=0/106, through 24 weeks).[5–7]

†GEMINI I and II are two identical 148-week, phase III, randomised, double-blind, multicentre, parallel-group, non-inferiority, controlled clinical trials testing the efficacy of DTG/3TC in treatment-naïve patients. Participants with screening HIV-1 RNA ≤500,000 copies/mL were randomised 1:1 to once-daily DTG/3TC (n=716, pooled) or DTG + TDF/FTC (n=717, pooled). The primary endpoint of each GEMINI study was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[13]

‡STAT is a phase IIIb, open-label, 48-week, single-arm pilot study evaluating the feasibility, efficacy, and safety of DTG/3TC in 131 newly diagnosed HIV-1 infected adults as a first line regimen. The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 24.[6]

§D2ARLING is a randomised, open-label, phase IV study designed to assess the efficacy and safety of DTG/3TC in treatment-naïve people with HIV with no available baseline HIV-1 resistance testing. Participants were randomised in a 1:1 ratio to receive DTG/3TC (n=106) or DTG + TDF/XTC (n=108). The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at Week 48.[7] Results at week 24 of the study.

||The reported rate reflects the sum-total of resistance cases calculated from TANGO (n=0/369, through 196 weeks) and SALSA (n=0/246, through 48 weeks).[8,9]

¶TANGO is a randomised, open-label, trial testing the efficacy of DOVATO in virologically suppressed patients. Participants were randomised in a 1:1 ratio to receive DOVATO (n=369) or continue with TAF-containing regimens (n=372) for up to 200 weeks. At Week 148, 298 of those on TAF-based regimens switched to DOVATO. The primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL (virologic non-response) as per the FDA Snapshot category at Week 48 (adjusted for randomisation stratification factor).[8,13]

#SALSA is a phase III, randomised, open-label, non-inferiority clinical trial evaluating the efficacy and safety of switching to DTG/3TC compared with continuing current antiretroviral regimens in virologically suppressed adults with HIV. Eligible participants were randomised 1:1 to switch to once-daily DTG/3TC (n=246) or continue current antiretroviral regimens (n=247). The primary endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 copies/mL at Week 48 (ITT-E population, snapshot algorithm).[9]

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